

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International BureauBA  
SH  
Dottach

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)



(51) International Patent Classification 5 :  C07K 7/00, 15/06, C12N 15/12	A1	(11) International Publication Number: WO 94/05695  (43) International Publication Date: 17 March 1994 (17.03.94)
(21) International Application Number: PCT/US93/08528  (22) International Filing Date: 9 September 1993 (09.09.93)		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
(30) Priority data: 943,236 10 September 1992 (10.09.92) US		Published <i>With international search report.</i>
(71) Applicant: NEW YORK UNIVERSITY [US/US]; 550 First Avenue, Rm. MSB-153, New York, NY 10016 (US).		
(72) Inventors: MURPHY, Randall, B. ; Riverview Road, Irvington, NY 10533 (US). SCHUSTER, David, I. ; 61 Signal Hill Road, Wilton, CT 06897 (US).		
(74) Agent: TOWNSEND, G., Kevin; Browdy and Neimark, 419 Seventh Street, N.W., Suite 300, Washington, DC 20004 (US).		
(54) Title: POLYPEPTIDES OF G-COUPLED RECEPTOR PROTEINS, AND COMPOSITIONS AND METHODS THEREOF		
(57) Abstract	<p>Compounds, compositions and methods involving purified, isolated and/or synthetic G-protein coupled receptor (GPR) polypeptides that comprise fragments, derivatives and/or consensus peptides of transmembrane domains of G-coupled receptor proteins, wherein the GPR polypeptide has biological activity selected from binding of a GPR ligand to a GPR or modulating the binding of GPR a ligand to a GPR.</p>	

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BC	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				



1  
**POLYPEPTIDES OF G-COUPLED RECEPTOR PROTEINS,  
AND COMPOSITIONS AND METHODS THEREOF**

**FIELD OF THE INVENTION**

The present invention relates to compounds, compositions and methods involving synthetic, isolated and/or recombinant G-protein coupled receptor polypeptides that comprise fragments and/or consensus peptides of G-protein coupled receptors.

**BACKGROUND OF THE INVENTION**

10       The membrane protein gene superfamily of G-protein coupled receptors (GPRs) has been characterized as having seven putative transmembrane domains. The domains are believed to represent transmembrane  $\alpha$ -helices connected by extracellular or cytoplasmic loops. Of the 74 sequenced members of this 15       G-protein receptor superfamily, the shortest sequence of 324 amino acids represents the rat *mas* oncogene and the longest, of 744 amino acids, represents the human thyroid-stimulating hormone (TSH) receptor. GPRs thus include a wide range of biologically active receptors, such as hormone-, viral-, growth 20       factor- and neuroreceptors.

25       G-protein coupled receptors have been characterized as including these seven conserved hydrophobic stretches of about 20-30 amino acids, connecting at least 8 divergent hydrophilic loops. The G-protein family of coupled receptors includes 30       dopamine receptors which bind in a noncovalent but high affinity manner to neuroleptic drugs used for treating psychotic and neurological disorders. For example, the dopamine D<sub>2</sub> receptor includes these transmembrane domains, two of which (TM III and TM V; see below) have been implicated by site-selective mutagenesis to demonstrate functional association with D<sub>2</sub> ligands.

---

Transmembrane domains of G-protein coupled receptors are designated TM1, TM2, TM3, TM4, TM5, TM6 and TM7. TM4, TM5, TM6 and TM7 are the most highly conserved and are postulated to

- 2 -

provide sequences which impart biological activity to GPRs. Most GPRs have single conserved cysteine residues in each of the first two extracellular loops which form disulfide bonds that are believed to stabilize functional protein structure. TM3 is 5 also implicated in signal transduction.

Phosphorylation and lipidation (palmitylation or farnesylation) of cysteine residues can influence signal transduction of some GPRs. Most GPRs contain potential phosphorylation sites (e.g., serine or threonine residues) 10 within the third cytoplasmic loop and/or the carboxy terminus. For several GPRs, such as the  $\beta$ -adrenoreceptor, phosphorylation by protein kinase A and/or specific receptor kinases mediates receptor desensitization.

Non-limiting examples of GPRs include cAMP receptors, 15 adenosine receptors,  $\beta$ -adrenergic receptors, muscarinic acetylcholine receptors,  $\alpha$ -adrenergic receptors, serotonin receptors (5-HT), histamine H<sub>2</sub> receptors, thrombin receptors, kinin receptors, follicle stimulating hormone receptors, opsins and rhodopsins, odorant receptors, cytomegalovirus receptor, 20 etc. See e.g., Probst et al *DNA and Cell Biology* 11:1-20 (1992), which is entirely incorporated herein by reference.

The ligand binding sites of GPRs are believed to comprise a hydrophilic socket formed by several GPR transmembrane domains, which socket is surrounded by hydrophobic 25 residues of the GPRs. The hydrophilic side of each GPR transmembrane helix is postulated to face inward and form the polar ligand binding site. TM3 has been implicated in several GPRs as having a ligand binding site, such as including the TM3 aspartate residue. Additionally, TM5 serines, a TM6 asparagine 30 and TM6 or TM7 phenylalanines or tyrosines are also implicated in ligand binding.

GPRs can be intracellularly coupled by heterotrimeric G-proteins to various intracellular enzymes, ion channels and transporters. See, e.g., Johnson et al *Endoc. Rev.* 35 10:317-331 (1989); and Birnbaumer et al *Biochem. Biophys. Acta* 1031:163-224 (1990) which references are incorporated entirely herein by reference. GPR agonist binding catalyzes the exchange

- 3 -

of GTP for GDP on the  $\alpha$ -subunit of the G-protein. Different G-protein  $\alpha$ -subunits preferentially stimulate particular effectors to modulate various biological functions in a cell. Phosphorylation of cytoplasmic residues of GPRs has been identified as an important mechanism for the regulation of G-protein coupling of some GPRs.

As a non-limiting example of a GPR ligand, dopamine (3,4-dihydroxyphenethylamine) is a critical neurotransmitter in the central nervous system (e.g., in the substantia nigra, midbrain, and hypothalamus). Since the elucidation of the ascending mesolimbic and nigrostriatal pathways, these pathways have been found to be critical in the control of both motor initiation (nigrostriatal) behavior and affective (mesolimbic) behavior. The clinical efficacy of the major neuroleptic antipsychotic medications has been found to correlate with the respective affinities of these agents for the dopamine D<sub>2</sub> receptor in the brain. A dopaminergic role in the symptomatology of the major psychoses has thus been hypothesized, although it is unclear if dopamine alone is etiological, (see, e.g., Davis et al. Am. J. Psych. 148:1474-1476 (1991)). Nonetheless, this hypothesis has served as a stimulus for current research in this area.

One model for studying possible interactions of G-protein coupled receptors with their ligands has emerged from site-directed mutagenesis and biochemical analysis of the  $\beta$ -adrenergic receptor, as well as from biophysical analysis of the interaction of retinal with opsin.

According to such a model, the binding of a GPR ligand to a G-protein coupled receptor involves multiple interactions between functional groups on the GPR ligand and residues within the hydrophophilic binding site of the receptor.

While a number of the amino acid residues in the dopamine D<sub>2</sub> receptor have been postulated to participate in D<sub>2</sub> ligand binding, based on results obtained from site-directed mutagenesis studies and photoaffinity labeling studies performed on the  $\beta$ -adrenergic receptor, such studies have failed to specifically determine which residues are actually involved in

- 4 -

binding in the D<sub>2</sub> system. Sibley et al. Soc. Neurosci. Abs. 17:36.10, 324.5, 324.6 (1991).

The clinical use of neuroleptics has provided a means for treating patients suffering from psychotic disorders.

5 Short-term use of neuroleptics is indicated in several types of psychotic disorders, e.g., acute psychotic episodes, regardless of type; exacerbations of schizophrenia; acute manic excitement while deferring use of lithium or awaiting onset of its effects; adjunctive therapy for major depression with prominent psychotic symptoms, or when an antidepressant or ECT alone is not successful; for agitation in delirium, dementia, or severe mental retardation while seeking to identify and treat the primary basis of the problem; in certain chronic, degenerative, or idiopathic neuropsychiatric disorders with dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome; or for ballism or hemiballism; childhood psychoses or apparently allied conditions marked by severe agitation or aggressive behavior; miscellaneous medical indications, notably nausea and vomiting, or intractable hiccups.

Additionally, continuous long-term use of neuroleptics is indicated in many psychotic disorders, such as (for more than six months) (i) primary indications such as Schizophrenia, Paranoia<sup>a,b</sup>, Childhood psychoses, some degenerative or idiopathic neuropsychiatric disorders (notably, Huntington's disease and Gilles de la Tourette's syndrome); (ii) secondary indications such as extremely unstable manic-depressive or other episodic psychoses (unusual), otherwise unmanageable behavior symptoms in dementia, amentia, or other brain syndromes; and (iii) questionable indications such as chronic characterological disorders with schizoid, "borderline," or neurotic characteristics; substance abuse; or antisocial behavior, recurrent mood disorders. See, e.g., Baldessarini, *Chemotherapy in Psychiatry*, Revised and Enlarged Edition, Harvard University Press, Cambridge, MA, (1985), the contents of which is entirely incorporated herein by reference.

Neuroleptics are also referred to as neuroleptics, psychopleptics, psycholeptics, antipsychotics and major

- 5 -

tranquilizers, but are sometimes distinguished from non-neuroleptic anti-psychotics. Neuroleptics have recently been characterized as an agent that produces sedative or tranquilizing effects, and which also produces motor side effects, such as catalepsy or extrapyramidal symptomatology. Nonlimiting representative examples of neuroleptics include phenothiazine derivatives (e.g., chlorpromazine); thioxanthine derivatives (e.g., thiothixene); butyrophenone derivatives (e.g., haloperidol); dihydroindolone (e.g., molindone); dibenzoxazepine derivatives (e.g., loxapine); and "atypical" neuroleptics (e.g., sulpiride, remoxipiride pimozide and clozapine). See Bernstein *Clinical Pharmacology* Littleton, Mass.:PSG Publishing (1978); Usdin et al *Clinical Pharmacology in Psychiatry* New York:Elsevier North-Holland (1981); and Baldessarini, *supra*, (1985); and , which references are herein entirely incorporated by reference.

The term "atypical neuroleptics" has been used to describe antipsychotic neuroleptics that produce few or no extrapyramidal side effects and which do not cause catalepsy in animals (See, e.g., Pickett et al, *Arch. Gen. Psychiatry* 49:345 (May 1992)). Alternatively, atypical neuroleptics, such as clozapine, have been described as those neuroleptics which have a higher affinity for D<sub>4</sub> and D<sub>5</sub> sites than for D<sub>2</sub> sites (See, e.g., Davis et al *Amer. J. Psych.* 148:1474, 1476 (November 1991)).

The long term use of all known anti-psychotics, such as neuroleptics or non-neuroleptic antipsychotics, has resulted in serious side effects, as present in Table I, such as persistent and poorly reversible motoric dysfunctions (e.g., tardive dyskinesia) in a significant number of patients. These side effects are especially prevalent in geriatric populations, and adequate pharmacological treatment of these debilitating motoric dysfunctions is not currently available. This problem has severely limited the long-term, clinical administration of  
these agents.

- 6 -

**TABLE I**  
**Neurological Side Effects of**  
**Neuroleptic-Antipsychotic Drugs**

Reaction	Features	Period of maximum risk	Proposed mechanism	Treatment
Acute dystonia	Spasm of muscles of tongue, face, neck, back; may mimic seizures; not hysterical	1-5 days	Dopamine excess? Acetylcholine excess?	Antiparkinsonism agents are diagnostic and curative (i.m. or i.v., then p.o.)
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask-facies, shuffling gait	5-30 days (rarely persists)	Dopamine blockade	Antiparkinsonism agents (p.o); dopamine agonists risky?
Akathisia	Motor restlessness; patient may experience anxiety or agitation	5-60 days (commonly persists)	Unknown	Reduce dose or change drug low doses of propranolol; antiparkinsonism agents or benzodiazepines may help
Tardive dyskinesia	Oral-facial dyskinesia; choreo-athetosis, sometimes irreversible, rarely progressive	6-24 months (worse on withdrawal)	Dopamine excess?	Prevention best; treatment unsatisfactory; slow spontaneous remission
"Rabbit" syndrome	Perioral tremor (late parkinsonism variant?); usually reversible	Months or years	Unknown	Antiparkinsonism agents; reduce dose of neuroleptic
Malignant syndrome	Catatonia, stupor, fever, unstable pulse and blood pressure; myoglobinemia; can be fatal	Weeks	Unknown	Stop neuroleptic; antiparkinsonism agents usually fail; bromocriptine often helps; dantrolene variable; general supportive care crucial

a. There may be an increased risk of hypotension on interacting high doses of propranolol with some antipsychotic agents; clonidine may also be effective at doses of 0.2-0.8 mg/day, but carries a high risk of hypotension (Zubenko et al., *Psychiatry Res.* 11:143, 1984).

In addition, clozapine, although apparently capable of producing less motor side effects, can cause irreversible, potentially fatal agranulocytosis in a minority of patients administered the drug. Such serious side effects limit the use of

7

clozapine to patients who are resistant to treatment with other neuroleptics.

Antipsychotics have a variety of significant pharmacological effects, e.g., as presented in the following Tables II and III.

**Table II**  
**Comparative Pharmacology of Neuroleptics**

Alkaloid Pharmacologic Actions	Phenothiazine Derivative Chlorpromazine	Thioxanthene Derivative Thiothixene	Butyrophenone Derivative Haloperidol
Antipsychotic	Yes + +	Yes + +	Yes + + + +
Antiemetic	Yes + + +	Not tested	Yes + + +
Hypothermia	Yes +	Yes +	No
Hypotension	Yes + +	Yes + + +	+
Parkinsonism	Yes + +	Yes +	Yes + + + +
Antiadrenergic	Yes + +	Yes + + +	+
Anticholinergic	Yes +	Yes +	Negligible
Antihistaminic	Yes +	Negligible	Negligible
Releases NE, DA	No	No	No
Blocks DA	Yes + +	Yes +	Yes + + + +
Blocks NE	Yes + +	Yes + + +	Yes +
Central sympathetic suppressant	Yes + +	Yes +	Yes + + +

Chlorpromazine, thiothixene, and haloperidol decrease the functional availability of dopamine (DA) and norepinephrine (NE) by blocking the dopamine receptor sites in the basal ganglia and norepinephrine receptor sites in thalamic and hypothalamic areas. Reserpine simply reduces the concentrations of norepinephrine and dopamine in these areas. Both of these actions result in suppression of central sympathetic activity.  
+ - + + + indicates from very weak to very strong effects.

**Table III**  
**Comparative Pharmacology of Antipsychotics**

Extrapyramidal Drug	Sedation	Adrenergic Blockage	Reaction
Chlorpromazine	High	Moderate to high	Moderate
Chlorprothixene	High	High	Low to moderate
Haloperidol	Low	Low	High
Molindone	Moderate	Moderate	Moderate to high
Loxapine	High	Low to moderate	High

See Ebadi, PHARMACOLOGY, Little, Brown and Co., Boston, 61-65 (1985); Cattabeni et al Adv. Biochem. Psychopharmacology 24:275 (1980). Baldessarini, supra, which references are herein incorporated entirely by reference.

5 However, despite the fact that thousands of neuroleptic- or antipsychotic-type compounds have been synthesized and reported in the literature, such compounds which lack serious side effects and which have sufficient pharmacological activity, have not been disclosed.

- 8 -

Alternative to dopamine receptor GPRs, as presented above, other neuroreceptor GPRs are involved in neurological pathologies, and drugs such as neuroreceptor GPR binding agents, presently used for treating these pathologies, also suffer from 5 similar side effects as those of neuroleptics, as presented above.

Other GPRs are also involved in receptor-related pathologies, such as hormone related GPRs involved in endocrine related pathologies.

Accordingly, there is a need to provide G-protein coupled 10 receptor binding agents, including neuroreceptor and endocrine receptor GPRs, which do not produce such deleterious and debilitating side effects as those produced by known agents, such as neuroleptics, which can be used for therapy or diagnosis of GPR related pathologies.

15 Citation of documents herein is not intended as an admission that any of the documents cited herein is pertinent prior art, or an admission that the cited documents are considered material to the patentability of the claims of the present application. All statements as to the date or representations as 20 to the contents of these documents are based on the information available to the applicant and does not constitute any admission as to the correctness of the dates or contents of these documents.

#### SUMMARY OF THE INVENTION

It is therefore an object of the present invention to 25 overcome one or more deficiencies found in the related art.

It is another object of the present invention to provide non-naturally occurring synthetic, isolated and/or recombinant GPR polypeptides which are fragments, consensus fragments and/or sequences having conservative amino acid substitutions, of at 30 least one transmembrane domain of at least one G-protein coupled receptor, which polypeptides have been discovered to have receptor-like functional binding sites of neuroreceptor and endocrine GPRs, such that GPR polypeptides of the present invention may bind GPR ligands, or which may also modulate, 35 quantitatively or qualitatively, GPR ligand binding to GPRs.

- 9 -

It is still another object of the present invention to provide GPR polypeptides and compositions that have only partially helical structures, in contrast to known characterized transmembrane domains of GPRs, such as, but not limited to, GPR 5 transmembrane domains I-VII.

It is yet another object of the present invention to provide synthetic or recombinant GPR polypeptides, conservative substitution derivatives thereof, antibodies, anti-idiotype antibodies, compositions and methods that can be used as potential 10 modulators of G-protein coupled receptor function, by binding to GPR ligands or modulate GPR ligand binding, due to their expected biological properties, which may be used in diagnostic, therapeutic and/or research applications.

It is a further object of the present invention is to 15 provide synthetic, isolated or recombinant polypeptides which are designed to inhibit or mimic various GPRs or fragments thereof, as receptor types and subtypes.

According to one aspect of the present invention, a synthetic or recombinant GPR polypeptide is provided that 20 comprises a GPR amino acid sequence of, e.g., at least 5, 10, 15 or 20 amino acids, substantially corresponding to at least one transmembrane domain, or fragment and/or consensus peptide thereof, of a G-protein coupled receptor, wherein at least 20 amino acids are preferred. In a preferred embodiment, the 25 polypeptide is (a) chemically synthesized and/or (b) obtained from a recombinant host cell or organism which expresses a recombinant nucleic acid encoding a GPR polypeptide, as defined herein.

In another preferred embodiment, the transmembrane domain is selected from at least one of TM1, TM2, TM3, TM4, TM5, TM6 or 30 TM7, corresponding to transmembrane domains I, II, III, IV, V, VI and VII, respectively, of a GPR. In another preferred embodiment, the transmembrane domain is a dopamine receptor transmembrane domain selected from the group consisting of at least one of a D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub> and D<sub>5</sub> dopamine receptor transmembrane domain. The

35 transmembrane domain, e.g., may be selected from at least one of D<sub>1</sub> receptor transmembrane domains III or V. In still another preferred embodiment, the GPR polypeptide amino acid sequence

- 10 -

substantially corresponding to an amino acid sequence contained in at least one of Fig. 2 (SEQ ID NO:2), Fig. 3 (SEQ ID NO:3) or Fig. 5 (SEQ ID NO:5).

In another aspect of the present invention, a GPR composition is provided, comprising a GPR polypeptide, or a pharmaceutically acceptable ester, ether, sulfate, carbonate, malate, glucuronide or salt thereof, the composition further comprising a pharmaceutically acceptable carrier and/or diluent.

In still another aspect of the present invention, a method is provided for treating a subject suffering from a disease state involving a qualitative or quantitative pathological abnormality of a GPR protein or a biological molecule functionally associated therewith. Such biological molecule may be a membrane cytoplasmic protein, lipid, carbohydrate, saccharide, nucleoside or nucleotide mono-, di-, or tri-phosphate, an enzyme, a co-factor, a nucleic acid, a neurotransmitter, an ion, a carrier, a cell receptor, or any combination thereof.

In a preferred embodiment, the GPR protein is a dopamine receptor and the abnormality involves a dopamine related pathology, wherein the method comprises administering an effective dopamine receptor modulating amount of a GPR polypeptide of the present invention. In another preferred embodiment, the transmembrane domain is a D<sub>2</sub> dopamine receptor domain and the disease state is a psychiatric disorder, such as schizophrenia or schiz affective disorder (see American Psychiatric Association, Revised Manual of Diagnostic and Statistical Criteria for Psychiatric Disorders (DSM-III-R), American Psychiatric Assoc. Press, Washington, DC (1989)).

In another preferred embodiment, the GPR composition is administered as a pharmaceutical composition to provide a GPR polypeptide in an amount ranging from about 0.01 µg to 100 mg/kg, and also preferably, about 10 µg to 10 mg/kg. In another preferred embodiment, the administering is by oral, intravenous, intramuscular, parenteral or topical administration, including mucosal administration to the nasal mucosa or the oral mucosa, by aerosol, nebulizer or drop administration as non-limiting examples.

- 11 -

Other objects of the invention will be apparent to skilled practitioners from the following detailed description and examples relating to the present invention.

5

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is the amino acid sequence of a control peptide (SEQ ID NO:1), which is hydrophobic in its properties, but does not correspond to a known GPR transmembrane domain.

Fig. 2 represents the amino acid sequence of a GPR 10 transmembrane polypeptide, polypeptide II (SEQ ID NO:2), which corresponds to a portion of the dopamine D<sub>1</sub> receptor transmembrane segment III.

Fig. 3 represents the amino acid sequence of a transmembrane polypeptide, polypeptide III (SEQ ID NO:3), 15 corresponding to a consensus peptide of the dopamine D<sub>1</sub> receptor transmembrane domains I-VII.

Fig. 4 represents the amino acid sequence of a consensus sequence of transmembrane domains that is shortened to be less than the length required to span a lipid bilayer.

Fig. 5 represents a consensus amino acid sequence of transmembrane domain as a consensus peptide between dopamine receptors D<sub>1</sub> and D<sub>2</sub>.

Fig. 6 is a representation of a circular dichroism spectrum of a solution of the consensus polypeptide III (SEQ ID NO:3) of Fig. 3.

Fig. 7 is a graphical representation of radioligand binding assay data comparing control polypeptide II (SEQ ID NO:1) of Fig. 1, labeled as "II" and consensus polypeptide I (SEQ ID NO:3) of Fig. 3, labeled as "I".

Fig. 8A-G are a comparison listing of amino acid sequences of transmembrane domains and adjacent amino acid sequences of representative GPRs (SEQ ID NOS:6-79).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention relates to G-protein coupled receptor (GPR) polypeptides which can be used to mimic naturally occurring or isolated GPRs, or to modulate the binding of GPR ligands to GPRs, such as inhibition or enhancement of binding.

5 GPR polypeptides of the present invention can include GPR transmembrane domain fragments and/or consensus peptides thereof, of at least 4-10 amino acids in length, and/or corresponding sequences having conservative amino acid substitutions as

10 "substitution peptides", wherein the GPR polypeptide binds a GPR ligand or modulates the binding of a GPR ligand to a GPR *in vitro*, *in vivo* or *in situ*.

GPR polypeptides of the present invention can be synthesized or recombinantly produced, or optionally purified, to

15 provide commercially useful amounts of GPR polypeptides for use in therapeutic, diagnostic or research applications, according to known method steps, see, e.g., Ausubel et al, eds. Current Protocols in Molecular Biology, Wiley Interscience, N.Y., (1987, 1992); and Sambrook et al, Molecular Cloning. A Laboratory Manual,

20 2nd edition, Vols. 1-3, Cold Spring Harbor Press, (1989), which references are herein entirely incorporated by reference.

Additionally, GPR polypeptides according to the present invention can be used to generate polyclonal and/or monoclonal antibodies, anti-idiotype antibodies thereto, or fragments

25 thereof, which may be used for diagnostic and/or therapeutic applications, according to known method steps, see, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Press (1988), which is herein entirely incorporated by reference.

GPR polypeptides, anti-GPR antibodies or anti-idiotype

30 antibodies (or fragments thereof) to GPR polypeptides have been unexpectedly discovered to quantitatively or qualitatively modulate G-protein coupled receptors, such that binding of GPR polypeptides or anti-idiotype antibodies (or fragments thereof) to G-protein coupled receptor ligands may be used for diagnostic

35 research or therapeutic applications of the present invention. Such GPR polypeptides, antibodies or anti-idiotype antibodies of the present invention may therefore be used as modulators of

- 13 -

G-protein coupled receptors, such as neuroreceptors or endocrine receptors, as non-limiting examples.

Binding of such GPR polypeptides, (including GPR fragments, consensus peptides, substitution derivatives and anti-  
5 idiotype antibody fragments) of the present invention may be used to treat symptoms of, and provide diagnosis and treatment for, pathologies related to GPRs. Such pathologies have been found to correlate with symptoms occurring in neurological, viral or endocrine pathologies. D<sub>2</sub> receptor-related psychotic disorders,  
10 including schizophrenia, now treated with neuroleptics, is a non-limiting example thereof.

The use of synthetic or recombinant GPR polypeptides of the present invention can be preferable to the use of known drugs that bind G-protein coupled receptors, such as neuroleptics that  
15 bind or inhibit the biological effect of binding to neuroreceptors as a non-limiting example. Such polypeptides are expected to have significantly less side effects than presently used drugs presently used for inhibiting such receptor binding including neuroleptics, as they would structurally mimic naturally occurring  
20 GPRs and/or modulate ligand binding. Thus, GPR polypeptides are expected to have reduced side effects attributable to known foreign compound drugs, with less immunogenicity, and reduced potential for motoric side effects (e.g., extrapyramidal symptoms and/or tardive dyskinesia).

25 The present invention is also related to the production, by chemical synthesis or recombinant DNA technology, of GPR polypeptides, preferably as small as possible while still retaining sufficiently high affinity or interaction with G-protein coupled receptors to modulate, such as to inhibit or to enhance,  
30 binding to such receptors by GPR ligands.

GPR polypeptides of the present invention may include 5-  
10 to 50-150 amino acid fragments, consensus sequences or substitution sequences of GPRs, e.g., as presented in Fig. 8A-G (SEQ ID NOS:6-79) including, but not limited to, multiple dopamine  
35 receptors, cAMP receptors, adenosine receptors, β-adrenergic receptors, muscarinic acetylcholine receptors, α-adrenergic receptors, serotonin receptors (5-HT), histamine H<sub>2</sub> receptors,

- 14 -

thrombin receptors, kinin receptors, follicle stimulating hormone receptors, opsins and rhodopsins, odorant receptors, cytomegalovirus GPRs, adenosine A2 receptors, dopamine receptor, histamine H2 receptors, octopanmine receptors, N-formyl receptors, 5 anaphylatoxin receptors, thromboxane receptors, IL-8 receptors, platelet activating factor receptors, endothelin receptors, bombesin gastrin releasing peptide receptor, neuromedin B preferring bombesin receptors, vasoactive intestinal peptides, neurotensin receptors, bradykinin receptors, thyrotropin-releasing 10 hormone receptors, substance P receptors, neuromedin K receptors, adrenal angiotensin II type I receptors, mas oncogene (angiotensin) receptors lutropin-choriogonadotropin receptors, thyrotropin receptors, follicle stimulating hormone receptors, cannabinoid receptors, glucocorticoid-induced receptors, 15 endothelial cell GPRs, testis GPRs, and thoracic aorta GPRs, and homologs thereof having a homology of at least 80% with at least one of transmembrane domains 1-7, as described herein. See, e.g., Probst et al *DNA and Cell Biology* 11:1-20(1992), which is entirely incorporated herein by reference.

20 Accordingly, a "G-protein coupled receptor polypeptide" or "GPR polypeptide" of the present invention includes polypeptides having a "GPR amino acid sequence" which substantially corresponds to at least one 10 to 50 amino acid fragment and/or consensus sequence of a known GPR or group of 25 GPRs, wherein the GPR polypeptide has homology of at least 80%, such as 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% homology, while maintaining GPR modulating activity, wherein a GPR polypeptide of the present invention is not naturally occurring or is naturally occurring but 30 is in a purified or isolated form which does not occur in nature. Preferably, a GPR polypeptide of the present invention substantially corresponds to a transmembrane domain of a GPR or group of GPRs as a consensus sequence.

Also preferred are GPR polypeptides wherein the GPR amino 35 acid sequence is 4-10 to 50 amino acids in length, such as 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39,

- 15 -

40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 60, 70, 80, 90, 100,  
110, 120, 130, 140 or 150 amino acids, or any range therein.

An amino acid or nucleic acid sequence of a GPR polypeptide of the present invention is said to "substantially correspond" to another amino acid or nucleic acid sequence, respectively, if the sequence of amino acids or nucleic acid in both molecules provides polypeptides having biological activity that is substantially similar, qualitatively or quantitatively, to the corresponding fragment of at least one GPR transmembrane domain, or which may be synergistic when two or more transmembrane domains, consensus sequences or homologs thereof are present.

Additionally or alternatively, such "substantially corresponding" sequences of GPR polypeptides include conservative amino acid or nucleotide substitutions, or degenerate nucleotide codon substitutions wherein individual amino acid or nucleotide substitutions are well known in the art.

Alternatively or additionally, substantially corresponding refers to GPR polypeptides having amino acid sequences having at least 80% homology or identity to an amino acid sequence of SEQ ID NO:1, such as 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% homology or identity.

Accordingly, GPR polypeptides of the present invention, or nucleic acid encoding therefor, include a finite set of substantially corresponding sequences as substitution peptides or polynucleotides which can be routinely obtained by one of ordinary skill in the art, without undue experimentation, based on the teachings and guidance presented herein. For a detailed description of protein chemistry and structure, see Schulz, G.E. et al., *Principles of Protein Structure*, Springer-Verlag, New York, 1978, and Creighton, T.E., *Proteins: Structure and Molecular Properties*, W.H. Freeman & Co., San Francisco, 1983, which are hereby incorporated by reference. For a presentation of nucleotide sequence substitutions, such as codon preferences, see Ausubel et al, *supra*, at §§ A.1.1-A.1.24, and Sambrook et al, *supra*, at Appendices C and D.

- 16 -

Conservative substitutions of a GPR polypeptide of the present invention includes a variant wherein at least one amino acid residue in the polypeptide has been conservatively replaced by a different amino acid. Such substitutions preferably are made 5 in accordance with the following list as presented in Table IV, which substitutions may be determined by routine experimentation to provide modified structural and functional properties of a synthesized polypeptide molecule, while maintaining the receptor binding, inhibiting or mimicking biological activity, as 10 determined by known GPR receptor activity assays.

Table IV

<u>Original Residue</u>	<u>Exemplary Substitution</u>
Ala	Gly;Ser
Arg	Lys
Asn	Gln;His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Ala;Pro
His	Asn;Gln
Ile	Leu;Val
Leu	Ile;Val
Lys	Arg;Gln;Glu
Met	Leu;Tyr;Ile
Phe	Met;Leu;Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp;Phe
Val	Ile;Leu

Alternatively, another group of substitutions of GPR polypeptides of the present invention are those in which at least one amino acid residue in the protein molecule has been removed and a different residue inserted in its place according to the following 5 Table V. The types of substitutions which may be made in the protein or peptide molecule of the present invention may be based on analysis of the frequencies of amino acid changes between a homologous protein of different species, such as those presented in Table 1-2 of Schulz et al., supra and Figs. 3-9 of Creighton, supra.

- 17 -

Based on such an analysis, alternative conservative substitutions are defined herein as exchanges within one of the following five groups:

TABLE V

1. Small aliphatic, nonpolar or slightly polar residues: Ala, Ser, Thr (Pro, Gly);
2. Polar, negatively charged residues and their amides: Asp, Asn, Glu, Gln;
3. Polar, positively charged residues: His, Arg, Lys;
4. Large aliphatic, nonpolar residues: Met, Leu, Ile, Val (Cys); and
5. Large aromatic residues: Phe, Tyr, Trp.

The three amino acid residues in parentheses above have special roles in protein architecture. Gly is the only residue lacking any side chain and thus imparts flexibility to the chain. This however tends to promote the formation of secondary structure 5 other than  $\alpha$ -helical. Pro, because of its unusual geometry, tightly constrains the chain. It generally tends to promote  $\beta$ -turn-like structures, although in some cases Cys can be capable of participating in disulfide bond formation which is important in protein folding. Note the Schulz *et al.* would merge Groups 1 and 2, 10 above. Note also that Tyr, because of its hydrogen bonding potential, has significant kinship with Ser, and Thr, etc.

Conservative amino acid substitutions according to the present invention, e.g., as presented above, are known in the art and would be expected to maintain biological and structural properties 15 of the polypeptide after amino acid substitution. Most deletions and insertions, and substitutions according to the present invention are those which do not produce radical changes in the characteristics of the protein or peptide molecule. "Characteristics" is defined in a non-inclusive manner to define both changes in secondary structure, 20 e.g.  $\alpha$ -helix or  $\beta$ -sheet, as well as changes in physiological activity, e.g. in receptor binding assays.

However, when the exact effect of the substitution, deletion, or insertion is to be confirmed one skilled in the art will appreciate that the effect of the substitution or substitutions will 25 be evaluated by routine screening assays, either immunoassays or bioassays to confirm biological activity, such as receptor binding or modulation of ligand binding to the corresponding GPR. See, e.g., Maranges *et al.*, *eds.*, for example, a substituted polypeptide

- 18 -

typically is made by site-specific mutagenesis of the peptide molecule-encoding nucleic acid, expression of the mutant nucleic acid in recombinant cell culture, and, optionally, purification from the cell culture, for example, by immunoaffinity chromatography using a 5 specific antibody on a chemically derivatized column or immobilized membranes or hollow fibers (to absorb the mutant by binding to at least one epitope).

A preferred use of this invention is the production, by chemical or recombinant DNA technology, of GPR polypeptides, 10 preferably as small as possible while still retaining sufficiently high affinity for binding to, or association with, GPRs. By production of GPR polypeptides including smaller fragments or variants of such transmembrane domains, one skilled in the art, using known binding and inhibition assays, can readily identify the GPR 15 polypeptides capable of binding minimizing or modulating G-protein coupled receptors using known methods. Non-limiting examples of fragments of GPRs to be used as GPR polypeptides or as a basis for consensus sequences thereof for GPR polypeptides, are presented in Figs. 2-5 and Fig. 8A-G, wherein fragments or consensus sequences of 20 10 to 50 amino acids of at least one sequence of Figs. 2-5 or corresponding to at least one transmembrane domain or domains 1-7 listed in Fig. 8A-G (SEQ ID NOS:6-79) are encompassed by the present invention, such as at least one transmembrane domain of one or more GPRs, such as a cAMP receptor (1), adenosine receptors (2-3); 25 muscarinic acetylcholine receptors (4-8); human adrenergic receptors (9-11, 14-16, 19-25, 28); adrenergic receptors (9-28); human thrombin receptor (31); endothelin receptors (35-36), bombesin receptors (37-38), endocrine receptors (48-50), rhodopsin (51). opsins (52-54), odorant receptors (55-64), and cytomegalovirus GPRs (72-54), as non- 30 limiting examples, wherein ("#") refers to the listed sequences in Fig. 8A-G.

Accordingly, GPR polypeptides may include consensus sequences and/or fragments of at least one of transmembrane domain 1-7 of one or more GPRs as presented in Figs. 2-5 (SEQ ID NO:2-5) or 35 Fig. 8A-G. (SEQ ID NOS:6-79) or homologs thereof, which GPR polypeptides do not occur naturally, and/or which are provided in an isolated and/or purified form not found in nature.

- 19 -

Consensus peptides of GPR polypeptides of the present invention may include peptides which are distinct from known GPR sequences in critical structural features, but which are derived from consensus sequences of homologous GPR transmembrane domains 1-7, 5 e.g., as presented in Fig. 8A-G (SEQ ID NOS:6-79). Such consensus peptides may be derived by molecular modeling, optionally combined with hydrophobicity analysis and/or fitting to model helices, as non-limiting examples. Such modeling can be accomplished according to known method steps using known modeling algorithms, such as, but 10 not limited to, ECEPP, INSIGHT, DISCOVER, CHEM-DRAW, AMBER, FRODO and CHEM-X. Such algorithms compare transmembrane domains between related G-protein coupled receptors, determine probable energy-minimized structures and define alternative consensus polypeptide fragments.

15 Such consensus peptides or fragments of GPRs may then be synthesized or produced recombinantly, in order to provide GPR polypeptides according to the present invention which mimic, modulate or inhibit binding of ligands to G-protein coupled receptors. GPR ligands, in the context of the present invention, refer to biological 20 molecules that bind GPRs *in vitro*, *in situ* or *in vivo*, and may include hormones, neurotransmitters, viruses or receptor binding domains, thereof, opsins, rhodopsins, nucleosides, nucleotides, coagulation cascade factors, odorants or pheromones, toxins, colony stimulating factors, platelet activating factors, neuroactive 25 peptides, neurohumors, or any biologically active compounds, such as drugs or synthetic or naturally occurring compounds.

The following non-limiting examples of consensus peptides of GPRs of the present invention are provided by way of guidance and not by way of limitation. In GPR polypeptides of the present 30 invention, one or more, preferably 4-10, Asp and/or Lys residues may additionally be incorporated at the carboxy and/or amino terminal ends in order to provide expected helix forming effects of the helix dipole effect, e.g., as described in Baldwin et al *Biochem.* 28:2130 (1989); Baldwin et al *Proc. Nat'l Acad. Sci. USA* 84:8898 (1987); and 35 Baldwin et al *Proc. Nat'l Acad. Sci. USA* 86:5286 (1989), which references are entirely incorporated herein by reference.

- 20 -

As a non-limiting example of GPR polypeptide of the present invention, dopamine receptor transmembrane fragments of D<sub>2</sub> transmembrane domain (e.g., domain III) as presented in Fig. 2 (SEQ ID NO:2) or a consensus sequence as presented in Fig. 3 (SEQ ID NO:3), e.g., of D<sub>2</sub> domains I-VII. Additionally or alternatively a consensus sequence may include less than 20 amino acids, such as 15 amino acids corresponding to a transmembrane domain, such as a D<sub>2</sub> receptor domain, as presented in Fig. 4 (SEQ ID NO:4) as polypeptide IV, which is smaller than the length required by spanning an average 10 lipid bilayer of a cell membrane.

However, in the context of the present invention, GPR polypeptides of greater than 15 -20 amino acids are preferred such that the GPR polypeptides are able to span the lipid bilayer.

Another non-limiting example of a GPR polypeptide using 15 dopamine receptor transmembrane domains is a consensus sequence of two or more GPR receptors, such as the dopamine D<sub>1</sub> and D<sub>2</sub> receptors. A non-limiting example of such a consensus GPR polypeptide is presented in Fig. 5 (SEQ ID NO:5).

Additionally, modified amino acids or chemical derivatives 20 of amino acids of consensus or fragments of GPRs proteins, according to the present invention may be provided, which polypeptides contain additional chemical moieties or modified amino acids not normally a part of the protein. Covalent modifications of the peptide are thus included within the scope of the present invention. Such 25 modifications may be introduced into a GPR polypeptide by reacting targeted amino acid residues of the polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or terminal residues. The following examples of chemical derivatives are provided by way of illustration and not by way of 30 limitation.

Aromatic amino acids may be replaced with D- or L-naphylalanine, D- or L-Phenylglycine, D- or L-2-thieneylalanine, D- or L-1-, 2-, 3- or 4-pyreneylalanine, D- or L-3-thieneylalanine, D- or L-(2-pyridinyl)-alanine, D- or L-(3-pyridinyl)-alanine, D- or 35 L-(2-pyrazinyl)-alanine, D- or L-(4-isopropyl)-phenylglycine, D-(trifluoromethyl)-phenylglycine, D-(trifluoromethyl)-phenylalanine, D-p-fluorophenylalanine, D- or L-p-biphenylphenylalanine, D- or

- 21 -

L-p-methoxybiphenylphenylalanine, D- or L-2-indole(alkyl)alanines, and D- or L-alkylainines where alkyl may be substituted or unsubstituted methyl, ethyl, propyl, hexyl, butyl, pentyl, iso-propyl, iso-butyl, sec-isotyl, iso-pentyl, non-acidic amino acids, 5 of C1-C20.

Acidic amino acids can be substituted with non-carboxylate amino acids while maintaining a negative charge, and derivatives or analogs thereof, such as the non-limiting examples of (phosphono)-alanine, glycine, leucine, isoleucine, threonine, or serine; or 10 sulfated (e.g., -SO<sub>3</sub>H) threonine, serine, tyrosine.

Other substitutions may include unnatural hydroxylated amino acids made by combining "alkyl" (as defined and exemplified herein) with any natural amino acid. Basic amino acids may be substituted with alkyl groups at any position of the naturally 15 occurring amino acids lysine, arginine, ornithine, citrulline, or (guanidino)-acetic acid, or other (guanidino)alkyl-acetic acids, where "alkyl" is defined as above. Nitrile derivatives (e.g., containing the CN-moiety in place of COOH) may also be substituted for asparagine or glutamine, and methionine sulfoxide may be 20 substituted for methionine. Methods of preparation of such peptide derivatives are well known to one skilled in the art.

In addition, any amide linkage in any of the GPR polypeptides can be replaced by a ketomethylene moiety, e.g. (-C(=O)-CH<sub>2</sub>-) for (-(C=O)-NH-). Such derivatives are expected to have the 25 property of increased stability to degradation by enzymes, and therefore possess advantages for the formulation of compounds which may have increased *in vivo* half lives, as administered by oral, intravenous, intramuscular, intraperitoneal, topical, rectal, intraocular, or other routes.

30 In addition, any amino acid representing a component of the said peptides can be replaced by the same amino acid but of the opposite chirality. Thus, any amino acid naturally occurring in the L-configuration (which may also be referred to as the R or S, depending upon the structure of the chemical entity) may be replaced

35 with an amino acid of the same chemical structural type, but of the opposite chirality, generally referred to as the D- amino acid but which can additionally be referred to as the R- or the S-, depending

upon its composition and chemical configuration. Such derivatives have the property of greatly increased stability to degradation by enzymes, and therefore are advantageous in the formulation of compounds which may have longer *in vivo* half lives, when 5 administered by oral, intravenous, intramuscular, intraperitoneal, topical, rectal, intraocular, or other routes.

Additional amino acid modifications of amino acids of GPR polypeptides of to the present invention may include the following: Cysteinyl residues may be reacted with alpha-haloacetates (and 10 corresponding amines), such as 2-chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteinyl residues may also be derivatized by reaction with compounds such as bromotrifluoroacetone, alpha-bromo-beta-(5-imidozoyl)propionic acid, chloroacetyl phosphate, 15 N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

Histidyl residues may be derivatized by reaction with compounds such as diethylprocarbonate e.g., at pH 5.5-7.0 because 20 this agent is relatively specific for the histidyl side chain, and para-bromophenacyl bromide may also be used; e.g., where the reaction is preferably performed in 0.1 M sodium cacodylate at pH 6.0.

Lysinyl and amino terminal residues may be reacted with compounds such as succinic or other carboxylic acid anhydrides. 25 Derivatization with these agents is expected to have the effect of reversing the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include compounds such as imidoesters/e.g., as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; 30 trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginyl residues may be modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin according to 35 known method steps. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these

- 23 -

reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

The specific modification of tyrosyl residues per se is well-known, such as for introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetrannitromethane. N-acetylimidizol and tetrannitromethane may be used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

Carboxyl side groups (aspartyl or glutamyl) may be selectively modified by reaction with carbodiimides ( $R'N-C-N-R'$ ) such as 1-cyclohexyl-3-(2-morpholinyl-(4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues may be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Glutaminyl and asparaginyl residues may be frequently deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues may be deamidated under mildly acidic conditions. Either form of these residues falls within the scope of the present invention.

Derivatization with bifunctional agents is useful for cross-linking the peptide to a water-insoluble support matrix or to other macromolecular carriers, according to known method steps. Commonly used cross-linking agents include, e.g.,

1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, 25 N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane.

Derivatizing agents such as 30 methyl-3-[(*p*-azidophenyl)dithio]propioimidate yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Patent Nos. 3,969,287; 3,691,016; 4,195,128;

35 4,247,642; 4,229,537; and 4,330,440 (which are herein incorporated entirely by reference), may be employed for protein immobilization.

- 24 -

Other modifications of GPR polypeptides of the present invention may include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T.E. Creighton, *Proteins: Structure and Molecule Properties*, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)), acetylation of the N-terminal amine, methylation of main chain amide residues (or substitution with N-methyl amino acids) and, in some instances, amidation of the C-terminal carboxyl groups, according to known method steps.

Such derivatized moieties may improve the solubility, absorption, permeability across the blood brain barrier biological half life, and the like. Such moieties or modifications of GPR polypeptides may alternatively eliminate or attenuate any possible undesirable side effect of the protein and the like. Moieties capable of mediating such effects are disclosed for example, in Remington's *Pharmaceutical Sciences*, 16th ed., Mack Publishing Co., Easton, PA (1980).

Such chemical derivatives of GPR polypeptides also may provide attachment to solid supports, including but not limited to, agarose, cellulose, hollow fibers, or other polymeric carbohydrates such as agarose, cellulose, such as for purification, generation of antibodies or cloning; or to provide altered physical properties, such as resistance to enzymatic degradation or increased binding affinity or modulation for GPRs, which is desired for therapeutic compositions comprising GPR polypeptides, antibodies thereto or fragments thereof. Such peptide derivatives are well-known in the art, as well as method steps for making such derivatives using carbodiimides active esters of N-hydroxy succinimide, or mixed anhydrides, as non-limiting examples.

Variation upon consensus peptide sequences of GPR polypeptide of the present invention may also include: the addition of one, two, three, four, or five lysine, arginine or other basic residues added to the -COOH terminal end of the peptide; and/or one, two, three, four, or five glutamate or aspartate or other acidic residues added to the amino terminal end of the peptide, where "acidic" and "basic" are as defined herein. Such modifications are

- 25 -

well known to increase the  $\alpha$ -helical content of the peptide by the "helix dipole effect". They also can provide enhanced aqueous solubility of the peptide. See, e.g., Baldwin et al., supra

As another non-limiting example of a GPR polypeptide of the present invention, serotonergic receptors (5-HT) consensus sequences may be determined using presently known 5-HT sequences and include, e.g., as consensus peptides of TM3, TM5 and TM7, respectively:

5-HT consensus (1) DDDDN IWSIFDWIGYLNSISMVIYTLFKKKK (SEQ ID NO:80)

5-HT consensus (2) DDDDN IWNIFSTIGYLNSISPVSIVMHIYGKKKK (SEQ ID NO:81)

10 5-HT consensus (3) DDDDG YSIYDTLVTFAINPVYITVFKKKK (SEQ ID NO:82)

Such non-naturally occurring consensus sequences may also be further modified according to known method steps to provide additional consensus peptides with substituted amino acids to increase or decrease  $\alpha$ -helical propensity and/or solubility (e.g., hydrophilicity). As a non-limiting example, 5-HT consensus peptide (1) above may be modified according to the present invention to have increased helical propensity and increased aqueous solubility as follows:

5-HT consensus (4) DDDDNAWSAFDWALYLNSISMAIYTYAKKKK (SEQ ID NO:83),

20 wherein, e.g., smaller, non-polar residues replace either larger, more polar residues (e.g., Ala for Ile or Val) or larger aromatic residues (e.g., Ala for Phe).

Another non-limiting, illustrative example of consensus GPR polypeptides of the present invention are those for adrenergic receptors, are the following:

An example of the consensus GPR polypeptide for domain VII across all presently known adrenergic receptors is as follows:

adrenergic consensus(1) LFSFITWLGYANSSLNPIIYTTF (SEQ ID NO:84)

30 An example of a consensus GPR polypeptide for domain V across all adrenergic receptors is as follows:

- 26 -

adrenergic consensus (2) VYTIYSSSVVFFAPSLAIMVITYT (SEQ ID NO:85)

Examples of a consensus GPR polypeptide for domain III across all adrenergic receptors are as follows:

adrenergic consensus (3) IWLTS DIMSTSSILHNLCVISF (SEQ ID NO:86)

5 An example of a consensus GPR polypeptide for domains III, V, and VII of all adrenergic receptors is as follows:

adrenergic consensus (4) IWSIFSSDIVVGYANHSSL AIMCPIVIYT (SEQ ID NO:87)

adrenergic consensus (5) IFTIFSSDIAVG YANHSSA AIMCPIVIYSV (SEQ ID NO:88),

Wherein variations and substitutions of amino acids may be made as  
10 described herein.

Non-limiting examples of consensus GPR polypeptides for transmembrane domain III across several or many, such as 1-500, or any range or value therein, G-protein receptors are as follows:

- TM3 - (1) YAIFVLYASAWLSFLNCPFIVTLNI (SEQ ID NO:96)
- 15 TM3 - (2) YAIFVLYATAWLSFLNCPFIVTLNI (SEQ ID NO:97)
- TM3 - (3) YAIFVLYATAWLTFLNCPFIVTLNI (SEQ ID NO:98)
- TM3 - (4) YAIFVLYASAWLTFLNCPFIVTLNI (SEQ ID NO:99)
- TM3 - (5) WAIFVLYASAWLSFLNCPFIVTLNI (SEQ ID NO:100)
- TM3 - (6) WAIFVLYATAWLSFLNCPFIVTLNI (SEQ ID NO:101)
- 20 TM3 - (7) WAIFVLYATAWLTFLNCPFIVTLNI (SEQ ID NO:102)
- TM3 - (8) WAIFVLYASAWLTFLNCPFIVTLNI (SEQ ID NO:103)
- TM3 - (9) YAVFVLYASAWLSFLNMPFIVTLNI (SEQ ID NO:104)
- TM3 - (10) YAVFVLYATAWLSFLNMPFIVTLNI (SEQ ID NO:105)
- TM3 - (11) YAVFVLYATAWLTFLNMPFIVTLNI (SEQ ID NO:106)
- 25 TM3 - (12) YAVFVLYASAWLTFLNMPFIVTLNI (SEQ ID NO:107)
- TM3 - (13) YAIFVLYASAWLSFLNCVTASIPFIVTLNI (SEQ ID NO:108)
- TM3 - (14) YAIFVLYASAWLSFLNCTSSIVVTASIVTLNI (SEQ ID NO:109)
- TM3 - (15) YAIFVLYASAWLSFLNVTLNICTSSIV (SEQ ID NO:110)
- TM3 - (16) YAIFVLYASAWLSFLNTASILNL MFIVTLNI (SEQ ID NO:111)
- 30 TM3 - (17) YAIFVLYASAWLSFLNMASILNLNP FIVTLNI (SEQ ID NO:112)
- TM3 - (18) YAIFVLYASAWLSFLNSGILLAPFIVTLNI (SEQ ID NO:113)
- TM3 - (19) YAIFVLYASAWLSFLNMSGILLAPFIVTLNI (SEQ ID NO:114)
- TM3 - (20) YAIFVLYASAWLSFLNSELSVYTLTVCPFIVTLNI (SEQ ID NO:115)
- TM3 - (21) YAIFVLYASAWLSFLNMSELSVYTLTVPFIVTLNI (SEQ ID NO:116)

- 27 -

- TM3 - (22) YAIFVLYASAWLASLSELSVYTLTVSFLNCPFIVTLNI (SEQ ID NO:117)  
TM3 - (23) YAIFVLYASAWLASLSELSVYTLTVPFIVTLNI (SEQ ID NO:118)  
TM3 - (24) YAIFVLYASAWLSFLASELSELSTLTTVNMPFIVTLNI (SEQ ID NO:119)  
TM3 - (25) YAIFVLYASAWLSFLNGGEIALWSLCPFIVTLNI (SEQ ID NO:120)  
5 TM3 - (26) YAIFVLYASAWLSFLNGGEIALWSLIVTLNI (SEQ ID NO:121)  
TM3 - (27) YAIFVLYASAWLGGEIALWSLNCPFIVTLNI (SEQ ID NO:122)  
TM3 - (28) YAIFVLYAGGEIALWSLSFLNCPFIVTLNI (SEQ ID NO:123)  
TM3 - (29) YAIFVLYASAWLSFFFLLFGYLGNFLLNCPFIVTLNI (SEQ ID NO:124)  
TM3 - (30) YAIFVLYASAWLFFFLLFGYLGNFLLPFIVTLNI (SEQ ID NO:125)  
10 TM3 - (31) YAIFVLYASAWLSFLNTACFYV рАITASLCFITEIALIPFIVTLNI (SEQ ID NO:126)  
TM3 - (32) YAIFVLYASAWLTACFYV рАITASLCFITEIALICPFIVTLNI (SEQ ID NO:127)  
TM3 - (33) YAIFVLYATACFYV рАITASLCFITEIALISFLNCPFIVTLNI (SEQ ID NO:128)  
TM3 - (34) YAITACFYV рАITASLCFITEIALIASAWLSFLNCPFIVTLNI (SEQ ID NO:129)  
TM3 - (35) YAIFVLYATACFYVAIITEIALISAWLSFLNCPFIVTLNI (SEQ ID NO:130)  
15 TM3 - (36) YAIFVLYASAWLSFLNACFYICLFAGVCFLIPFIVTLNI (SEQ ID NO:131)  
TM3 - (37) YAIFVLYASAWNACFYICLFAGVMFLILSFLNCPFIVTLNI (SEQ ID NO:132)  
TM3 - (38) YAIFVLYFYICLFAGVCFLIASAWLSFLNCPFIVTLNI (SEQ ID NO:133)  
TM3 - (39) YAIFVLYASVDAVNMFTSAWLSFLNCPFIVTLNI (SEQ ID NO:134)  
TM3 - (40) YAIFSVDAVNMFVLYASAWLSFLNCPFIVTLNI (SEQ ID NO:135)  
20 TM3 - (41) YAIFVLYASAWLSVDAVNMFSTSFLNCPFIVTLNI (SEQ ID NO:136)  
TM3 - (42) YAIFVLYASAWLSFLNSVDAVNMFPTFIVTLNI (SEQ ID NO:137)  
TM3 - (43) YAIFVLYASAWLSFLNCPFIVSVDAVNMFPTTLNI (SEQ ID NO:138)  
TM3 - (44) YAIFVLYASAWLSVDMFTSFLNCPFIVTLNI (SEQ ID NO:139)  
TM3 - (45) YAISVDAVNMFPTFVLYASAWLSFLNCPFIVTLNI (SEQ ID NO:140)  
25 TM3 - (46) YAIFSLSVFSLLAIVLYASAWLSFLNCPFIVTLNI (SEQ ID NO:141)  
TM3 - (47) YAIFVLYASLSVFSLLAISAWLSFLNCPFIVTLNI (SEQ ID NO:142)  
TM3 - (48) YAIFVLYASAWLSVFSLLAISFLNCPFIVTLNI (SEQ ID NO:143)  
TM3 - (49) YAIFVLYASAWLSFLSLSVFSLLAINCPFIVTLNI (SEQ ID NO:144)  
TM3 - (50) YAIFVLYASAWLSFLNPFFSLVSFLSLLAIIVTLNI (SEQ ID NO:145)  
30 TM3 - (51) YAIFVLYATAWLTFLNCVTATIPFIVTLNI (SEQ ID NO:146)  
TM3 - (52) YAIFVLYATAWLSFLNCTSSIVVTATIVTLNI (SEQ ID NO:147)  
TM3 - (53) YAIFVLYATAWLSFLNVTLNICTTTIV (SEQ ID NO:148)  
TM3 - (54) YAIFVLYATAWLTFLNTATIILNLMFIVTLNI (SEQ ID NO:149)  
TM3 - (55) YAIFVLYATAWLSFLNMMATIILNLPFIVTLNI (SEQ ID NO:150)  
35 TM3 - (56) YAIFVLYATAWLTFLNSGILLAPFIVTLNI (SEQ ID NO:151)  
TM3 - (57) YAIFVLYASAWLTFLNMTGILLAPFIVTLNI (SEQ ID NO:152)  
TM3 - (58) YAIFVLYASAWLTFLNTELTVYTLTVCPFIVTLNI (SEQ ID NO:153)  
TM3 - (59) YAIFVLYASAWLTFLNMTTELTVYTLTVPFIVTLNI (SEQ ID NO:154)  
TM3 - (60) YAIFVLYATAWLATELTVYTLTVFLNCPFIVTLNI (SEQ ID NO:155)  
40 TM3 - (61) YAIFVLYASAWLATELSVYTLTVPFIVTLNI (SEQ ID NO:156)  
TM3 - (62) YAIFVLYATAWLSFLATELSVYASELSTLTTVNMPFIVTLNI (SEQ ID NO:157)  
TM3 - (63) YAIFVLYATAWLSFLNGGEIALWTLCPFIVTLNI (SEQ ID NO:158)  
TM3 - (64) YAIFVLYASAWLTFLNGGEIALWTLIVTLNI (SEQ ID NO:159)  
TM3 - (65) YAIFVLYASAWLGGEIALWTLNCPFIVTLNI (SEQ ID NO:160)  
45 TM3 - (66) YAIFVLYAGGEIALWTLSFLNCPFIVTLNI (SEQ ID NO:161)

- 28 -

- TM3 - (67) YAIFVLYATAWLSFFFLLFGYLGNGFLNCPFIVTLNI (SEQ ID NO:162)
- TM3 - (68) YAIFVLYATAWLFLLFGYLGNGFLLPFIVTLNI (SEQ ID NO:163)
- TM3 - (69) YAIFVLYATAWLTLNTACFYVAITASLCFITEIALIPFIVTLNI (SEQ ID NO:164)
- TM3 - (70) YAIFVLYATAWLTCACFYVAITATLCFITEIALICPFIVTLNI (SEQ ID NO:165)
- 5 TM3 - (71) YAIFVLYATACFYVAITATLCFITEIALISFLNCPFIVTLNI (SEQ ID NO:166)
- TM3 - (72) YAITACFYVAITASLCFITEIALIAITAFLTFLNCPFIVTLNI (SEQ ID NO:167)
- TM3 - (73) YAIFVLYATACFYVAIITEIALITAWLTFLNCPFIVTLNI (SEQ ID NO:168)
- TM3 - (74) YAIFVLYASAWLTFLNACFYICLFAVGVCFLIPFIVTLNI (SEQ ID NO:169)
- TM3 - (75) YAIFVLYASAWNACFYICLFAGVMFLILTFLNCPFIVTLNI (SEQ ID NO:170)
- 10 TM3 - (76) YAIFVLYFYICLFAVCFLIATAWLTFLNCPFIVTLNI (SEQ ID NO:171)
- TM3 - (77) YAIFVLYATVDAVNMFTTAWLTFLNCPFIVTLNI (SEQ ID NO:172)
- TM3 - (78) YAIFTDAVNMFVLYATAWLTFLNCPFIVTLNI (SEQ ID NO:173)
- TM3 - (79) YAIFVLYATAWLTVDAVNMFTSFLNCPFIVTLNI (SEQ ID NO:174)
- TM3 - (80) YAIFVLYATAWLSFLNTVDAVNMFTPFLNCPFIVTLNI (SEQ ID NO:175)
- 15 TM3 - (81) YAIFVLYASAWLTFLNCPFIVSVDAVNMFITLNI (SEQ ID NO:176)
- TM3 - (82) YAIFVLYATAWLSVDMFTTFLNCPFIVTLNI (SEQ ID NO:177)
- TM3 - (83) YAISVDAVNMFVLYATAWLSFLNCPFIVTLNI (SEQ ID NO:178)
- TM3 - (84) YAIFVLYASLTVFSSLALIASAWLTFLNCPFIVTLNI (SEQ ID NO:179)
- TM3 - (85) YAIFVLYASAWLTLSVFTLLAISFLNCPFIVTLNI (SEQ ID NO:180)
- 20 TM3 - (86) YAIFVLYASAWLTFLSLSVFTLLAINCPFIVTLNI (SEQ ID NO:181)
- TM3 - (87) YAIFVLYASAWLTFLNPFSLSVFSLLAIIVTLNI (SEQ ID NO:182)
- TM3 - (88) YAIFVLYASAWLSFLNLGGVTASFTASVGPFIVTLNI (SEQ ID NO:183)
- TM3 - (89) YAIFVLYASAWLSFLNLGGVTASFTASVGVTLNI (SEQ ID NO:184)
- TM3 - (90) YAIFVLLGGVTASFTASVNYASAWLSFLNCPFIVTLNI (SEQ ID NO:185)
- 25 TM3 - (91) YAIFVLYAIFFFLLSFAWLSFLNCPFIVTLNI (SEQ ID NO:186)
- TM3 - (92) YAIFVLYASAWLSFLNCPFIVTLNIIFFFLLFIVTLNI (SEQ ID NO:187)
- TM3 - (93) YAIFVLYASAWIFFFLFLSFLNCPFIVTLNI (SEQ ID NO:188)
- TM3 - (94) YAIFVLYASAWLFFTVLASELSVYTLTVSFLNCPFIVTLNI (SEQ ID NO:189)
- TM3 - (95) YAIFVLYASAWLSFLFATLGGEIALCPFIVTLNI (SEQ ID NO:190)
- 30 TM3 - (96) YAIFVLYAFATLGGEIALSAWLSFLNCPFIVTLNI (SEQ ID NO:191)
- TM3 - (97) YAIFFTVLASELSVYTLTVYASAWLSFLNCPFIVTLNI (SEQ ID NO:192)
- TM3 - (98) YAIFFPPIAALFASTIASAWLSFLNCPFIVTLNI (SEQ ID NO:193)
- TM3 - (99) YAIFVLYASAWLSFPPIAALFASIPFIVTLNI (SEQ ID NO:194)
- TM3 - (100) YAIFVLYASAWLSFLNCPFFPIAALFASILNI (SEQ ID NO:195)
- 35 TM3 - (101) YAIFVLYASAWLSDLVLFSTASIMHLSFLNGGEIALWSLIVTLNI (SEQ ID NO:196)
- TM3 - (102) YAIFVLYASLDVLFSTASIMHLLIALWSLNCNFIVTLNI (SEQ ID NO:197)
- TM3 - (103) YAIFVLYAGGEIALWSLSFLNSLDVLFSTASIMHLPFIVTLNI (SEQ ID NO:198)
- TM3 - (104) YAIFVLYASAWLSFFDVLFSTASIMHLLFGYLGNGFLNCPFIVTLNI (SEQ ID NO:199)
- TM3 - (105) YAIFVLYASAWLFFFLFGYLSLDVLFSTASIMHLLGNFLLPFIVTLNI (SEQ ID NO:200)
- 40 TM3 - (106) YAIFVLYASAWLSFLNTACFYVAITASLSLMHLFITEIALIPFIVTLNI (SEQ ID NO:201)
- TM3 - (107) YASLDVLFSTAIMHLSAWLTACFYVAITASLCFITEIALICPFIVTLNI (SEQ ID NO:202)
- TM3 - (108) YAIFVLYATACFYVAITASLSFLNCPFIVTLNIISLDVLFSTASIMHL (SEQ ID NO:203)
- TM3 - (109) YAITACFYVAITASLCFITEIALIASAWLSFLNCPFIVTLNI (SEQ ID NO:204)
- TM3 - (110) YAIFVLYATACFYSTASILNLIMHLCAISLVAIITEIALISAWLSFLN (SEQ ID NO:205)
- 45 TM3 - (111) YAIFVLYASAWLSFLNACFYICLFA SILNLIMHLGVCFILPFIVTLNI (SEQ ID NO:206)

- 29 -

- TM3 - (112) YAIFVLYASAWNASIILNIMHLCFYICLFAGVMLILSFLNCPIVTLNI (SEQ ID NO: 207)  
TM3 - (113) YAIFPFVQCVVSIFSLVLIAVVLYFYIAGVCFLIASAFLSFLNCPIVTI (SEQ ID NO: 208)  
TM3 - (114) PFVQCVSITVSIFSLVLIAVYAIIFVLYASVDAVNMFTSAWCPFIVTLNI (SEQ ID NO: 209)  
TM3 - (115) YAIFGDWSSVDAVNMFVLYASAWLSFLNCPIVTLNI (SEQ ID NO: 210)  
5 TM3 - (116) YAIFVLYAGDWSSAWLSVDAVNMFTSFLNCPIVTLNI (SEQ ID NO: 211)  
TM3 - (117) YAIFVLYASAWLGDWSSFLNSVDAVNMFPTFIVTLNI (SEQ ID NO: 212)  
TM3 - (118) YAIFVLYASAWLSFLNCPIVGDWSSVDAVNMFPTLNI (SEQ ID NO: 213)  
TM3 - (119) YAIFVLYASAWLGYLGSVDMFTSFLNCPIVTGDSLNI (SEQ ID NO: 214)  
TM3 - (120) YAISVDAVNMFVLYAGYLGSAWLSFLNCPIVTLNI (SEQ ID NO: 215)  
10 TM3 - (121) YAIFSLSVFSLLAIVLYASAWLGYLGSFLNCPIVTLNI (SEQ ID NO: 216)  
TM3 - (122) YAIFVLYAGYLGAGNMDSLSVFSLLAISAWLSFLNCPIVTLNI (SEQ ID NO: 217)  
TM3 - (123) YAIFVLYASAWLSSLVFGNMSLLAISFLNCPIVTLNI (SEQ ID NO: 218)  
TM3 - (124) YAIFVLYASAWLSFLSSLVFGSLLAINCPIVTLNI (SEQ ID NO: 219)  
TM3 - (125) YAIFVLYASAWLSFLNPFSLSVFGSLLAIIVTLNI (SEQ ID NO: 220)  
15 TM3 - (126) YAIFVLYATAWLTFLSLANCVTATIPFIVTLNI (SEQ ID NO: 221)  
TM3 - (127) YAIFVLYATAWLSFLNCTSASSIVVTATIVTLNI (SEQ ID NO: 222)  
TM3 - (128) YAIFVLYATAWLSFLNVTLNISLACTTTIV (SEQ ID NO: 223)  
TM3 - (129) YAIFVLYATAWLTFLNTATILSLANLMFIVTLNI (SEQ ID NO: 224)  
TM3 - (130) YAIFVLYATAWLSFLNMATILNLPSVDAIVTLNI (SEQ ID NO: 225)

20 Recently discovered G-proteins also can be used according to the presently claimed invention to provide GPR polypeptides of the present invention, based on the teaching and guidance presented herein. Examples of such GPR polypeptides of the present invention may include, as non-limiting examples, GPR polypeptides corresponding  
25 to transmembrane domain III, e.g., as follows:

- TM3 - (131) ISTMYTVTGRWTLGQVVCDFWLSSDITCCTASILHLCVIAL (SEQ ID NO: 226)  
TM3 - (132) ILYGYRWPLPSKLCAVWIYLDVLFSTASIMHLCAISL (SEQ ID NO: 227)  
TM3 - (133) IIYI VMDRWKLGYFLCEWVLSVDMTCCTCSILHLCVIAL (SEQ ID NO: 228)  
TM3 - (134) IADKTVRVAMGAENDLGYNFRSDDVCGHCWQWYCSL (SEQ ID NO: 229)  
30 TM3 - (135) ILNYWPFGLALCHFVNYSQAVSVLVSAYTLVAISI (SEQ ID NO: 230)  
TM3 - (136) ILGRWEFGIHLCKLWLTCVDLCCCTSSILNLCAIALD (SEQ ID NO: 231)  
TM3 - (137) IMASVMHRHCLPLIGICLSSERHCLVSIFVELGAL (SEQ ID NO: 232)

Further non-limiting examples of consensus GPR polypeptides for transmembrane domain III of several or many, such as 1-500, or  
35 any range or value therein, more recently discovered G-protein receptors are as follows:

- TM3 - (138) YAIFVLYASAWLSFLNCPIFISILHLCVIALVTLNI (SEQ ID NO: 233)  
TM3 - (139) YAIFVLYATAWLSFLNCPIFISILNLCAIALDVTLNI (SEQ ID NO: 234)

- 30 -

- TM3 - (140) YAIFVLYATAWLTFLNCPFISIFVELGALVTLNI (SEQ ID NO: 235)  
 TM3 - (141) YAIFVLYASAWLTFLNCPFISIFVELSIMHLCAISLGA  
 TM3 - (142) WAIFVLYAILGRWEFGIHLCKLWLTSAWLSIMHLCAISLSFLNCPFIVTLNI (SEQ ID NO: 237)  
 TM3 - (143) WAIFVLYAILGRWEFGIHLCKLWLTAWSIMHLCAISLSFLNCPFIVTLNI (SEQ ID NO: 238)  
 5 TM3 - (144) WAIFVLYATAWLTFLNCPFSIMHLCAISLIVTLNI (SEQ ID NO: 239)  
 TM3 - (145) WAIFVLYASAWLTFLNCPFISIMHLCAISLVTLN  
 TM3 - (146) YAVFVLYASAWLSFLNMSIMHLCAISLPFIVTLNI (SEQ ID NO: 241)  
 TM3 - (147) YAVFVLYATAWLSFLNMPFSILNLCAIALDIVTLNI (SEQ ID NO: 242)  
 TM3 - (148) YAVFVLYATAWLSILNLCAIALDTFLNMPFIVTLNI (SEQ ID NO: 243)  
 10 TM3 - (149) YAVFVLYASILNLCAIALDSA  
 TM3 - (150) YAIFVLYASAWLSFLNCVTSIPFCLVSIFVELGALIVTLNI (SEQ ID NO: 245)  
 TM3 - (151) YAIFVLYASAWLSFLNCLVSIFVELGALIVVTASIVTLNI (SEQ ID NO: 246)  
 TM3 - (152) YAIFVLYASAWLSFLNVTLNCLVSIFVELGALII (SEQ ID NO: 247)  
 TM3 - (153) YAIFVLYASAWLSFLNTASILNLMFICLVSIFVELGALVTLNI (SEQ ID NO: 248)  
 15 TM3 - (154) YAIFVLYASAWLSFLNMASILNLPFCLVSIFVELGALVTLNI (SEQ ID NO: 249)  
 TM3 - (155) YAIFVLYASAWLSFLNILGRWEFGIHLCKLWLTCDVLCC  
 TM3 - (156) YAIFVLYASAWLSFLNMILGRWEFGIHLCKLWLTCDVLCC  
 TM3 - (157) YAIFVLYASAWLILGRWEFGIHLCKLWLTCDVLCC  
 NO: 252) 5  
 20 TM3 - (158) YAIFVLYAILGRWEFGIHLCKLWLTCDVLCC  
 NO: 253) 5  
 TM3 - (159) YAIFVLYASAWLASRWPLPLSVYTLTVSFLNCPFIVTLNI (SEQ ID NO: 254)  
 TM3 - (160) YAIFVLYASAWLASLILYYWRWPLPC  
 NO: 255) 5  
 25 TM3 - (161) YAIFVLYASAWLSFLASELSVYASELSSTLHD  
 NO: 256) 5  
 TM3 - (162) YAIFVLYASAWLSFLNGGEIALW  
 NO: 257) 5  
 TM3 - (163) YVWLWLDVFCC  
 30 TM3 - (164) YAIFVLYASAWLAIILYYWRWPLPC  
 NO: 259)

Non-limiting examples of consensus GPR polypeptides for domain V across several or many, such as 1-500, or any range or value therein, G-protein receptors are as follows:

- TMS - (1) CDVFVFVDIMLCTASIFNLCAISVG (SEQ ID NO: 260)  
 35 TMS - (2) YAIFVLYDIMLCTASIFNLCAISVG (SEQ ID NO: 261)  
 TMS - (3) DYAIFFVDIMLMTASIFNLMAISVG (SEQ ID NO: 262)  
 TMS - (4) DYAIFFVDIMLHTTASTIFNLMATITVG (SEQ ID NO: 263)  
 TMS - (5) CDVAVVYSSDIMALFYVCTASIFSSNLCAISSVG (SEQ ID NO: 264)  
 TMS - (6) FLFCSLGSFYIPIAVILVDIMLCTASIFNLCAISVG (SEQ ID NO: 265)  
 40 TMS - (7) YAIFVLYDFLFCSLGSFYIPIAVILIMLCTASIFNLCAISVG (SEQ ID NO: 266)  
 TMS - (8) DYAIFFVDIMLMTASIFLFCSLGSFYIPIAVILISVG (SEQ ID NO: 267)  
 TMS - (9) DYAIFFVDIMLHTTASTIFNLMAFLFCSLGSFYIPIAVILTITVG (SEQ ID NO: 268)

- 31 -

- TMS - (10) CDVAVVYSSDIMLFYVCTASIFSSNLFLFCSLGSFYCAISSVG (SEQ ID NO: 269)
- TMS - (11) CDVFVFDIMLCTASIFNWLSSIGSFFAPCLILLVYLCAISVG (SEQ ID NO: 270)
- TMS - (12) YAIFVLYDIMLCTASIFNLCAIWYISSLSSIGSFFAPCLILLVYLCAISVG (SEQ ID NO: 271)
- TMS - (13) DYAFVFVDIWLSSIGSFFAPCLILLVYLASIFNLMAISVG (SEQ ID NO: 272)
- 5 TMS - (14) DYAIWYIILSSIGSFFAPCLILLVYLIMLHTTASTIFNLMATITVG (SEQ ID NO: 273)
- TMS - (15) CDVAVVYSSDIMLFYVCWYIILSSIGSFFAPCLILLVYLSSNLCAISSVG (SEQ ID NO: 274)
- TMS - (16) CDVFVFDIMLCTASIFWYVISSSIGSFFAPCLINHLVYNLCAISVG (SEQ ID NO: 275)
- TMS - (17) YAIFVLYDIMLCTASIFNLCAIWYVISSSIGSFFAPCLINHLVYLVG (SEQ ID NO: 276)
- TMS - (18) DYAFVFVWYVISSSIGSFFAPCLINHLVYDMLMTASIFNLMAISVG (SEQ ID NO: 277)
- 10 TMS - (19) DYAFVFVDIMLHTTASTIFWYVISSSIGSFFAPCLINHLVYTIVG (SEQ ID NO: 278)
- TMS - (20) CDVAVVYSSDIMLFYVCTASIFSWYVISIGSFFAINHLVYNLCAISSVG (SEQ ID NO: 279)
- TMS - (21) CDVFVFDIMLCTASIFNLCAITYAISSVISFYIPVAILVTYT (SEQ ID NO: 280)
- TMS - (22) YAIFVLYDIMLCTATYAISSVISFYIPVAILVTYTTSIFNLCAISVG (SEQ ID NO: 281)
- TMS - (23) DYAFVFVDIMLMTATYAISSVISFYIPVAILVTYTISVG (SEQ ID NO: 282)
- 15 TMS - (24) TYAISSVISFYIPVATDYAFVFVDIMLHTTASTIFNLMATITVG (SEQ ID NO: 283)
- TMS - (25) CDVAVVYSSDIMLFYVCTATTYAISSVISFYIPVAILVTYTSSVG (SEQ ID NO: 284)
- TMS - (26) CDVFVFDVFIYSSVVSFYLPFGVTVLVLVYACTASIFNLCAISVG (SEQ ID NO: 285)
- TMS - (27) YAIFVLYDFVFIYSSVVSFYLPFGVTVLVLVYASIFNLCAISVG (SEQ ID NO: 286)
- TMS - (28) DYAFVFVDVFIYSSVVSFYLPFGVTVLVLVYATASIFNLMAISVG (SEQ ID NO: 287)
- 20 TMS - (29) DYAFVFVDVFIYSSVVSFYLPFGVTVLVLVYAHTTASTIFNLMATITVG (SEQ ID NO: 288)
- TMS - (30) CDVAVVYSSDFVFIYSSVVSFYLPFGVTVVCTASIFSSNLCAISSVG (SEQ ID NO: 289)
- TMS - (31) CDVFVFDIMLCTASYTIYSTCGAFYIPSVLLIILYGNLCAISVG (SEQ ID NO: 290)
- TMS - (32) YAIFVLYDIMLCTASYTIYSTCGAFYIPSVLLIILYGNLCAISVG (SEQ ID NO: 291)
- TMS - (33) DYAFVFVDIMLMTASYTIYSTCGAFYIPSVLLIILYGNLMAISVG (SEQ ID NO: 292)
- 25 TMS - (34) DYAFVFVDIMLHTTASYTIYSTCGAFYIPSVLLIILYGMATITVG (SEQ ID NO: 293)
- TMS - (35) CDVAVVYSSDIMSFTIYSTCGAFYIPSVLLIILYGFSSNLCAISSVG (SEQ ID NO: 294)
- TMS - (36) CDVFVFFVLIGSFVAVDIMLCTASIFNLCAISVG (SEQ ID NO: 295)
- TMS - (37) YAIFVLYFVLIGSFVADIMLCTASIFNLCAISVG (SEQ ID NO: 296)
- TMS - (38) DYAFVFVFVLIGSFVADIMLMTASIFNLMAISVG (SEQ ID NO: 297)
- 30 TMS - (39) DYAFVFVFVLIGSFVADIMLHTTASTIFNLMATITVG (SEQ ID NO: 298)
- TMS - (40) CDVAVVYSSFVLIGSFVADIMLFYVCTASIFSSNLCAISSVG (SEQ ID NO: 299)
- TMS - (41) CDVFVFDIMLCFFIPTLIMVITYFNLCALISVG (SEQ ID NO: 300)
- TMS - (42) YAIFVLYDIMLCFFIPTLIMVITYFNLCALISVG (SEQ ID NO: 301)
- TMS - (43) DYAFVFVDIMLMFFIPTLIMVITYFNLMATISVG (SEQ ID NO: 302)
- 35 TMS - (44) DYAFVFVDIMLHTFFFIPTLIMVITYFNLMATITVG (SEQ ID NO: 303)
- TMS - (45) CDVAVVYSSDIMLFYVCFPIPTLIMVITYFSSNLCAISSVG (SEQ ID NO: 304)
- TMS - (46) CDVYYGLVDGLVTFYLPPLLIMCITYYDIMLCTASIFNLCAISVG (SEQ ID NO: 305)
- TMS - (47) YAIVYGLVDGLVTFYLPPLLIMCITYYDIMLCTASIFNLCAISVG (SEQ ID NO: 306)
- TMS - (48) DYAFVYGLVDGLVTFYLPPLLIMCITYYDIMLMTASIFNLMAISVG (SEQ ID NO: 307)
- 40 TMS - (49) DYAFVYGLVDGLVTFYLPPLLIMCISSDIMLHTTASTIFNLMATITVG (SEQ ID NO: 308)
- TMS - (50) CDVYYGLVDGLVTFYLPPLLIMCITYYDIMLFYVCTASIFSSNLCAISSVG (SEQ ID NO: 309)
- TMS - (51) CDVFVFDIMLLVIFLGLVIVIPFVLIIVSYASIFNLCAISVG (SEQ ID NO: 310)
- TMS - (52) YAIFVLYDIMLLVIFLGLVIVIPFVLIIVSYAIFNLCAISVG (SEQ ID NO: 311)
- TMS - (53) DYAFVFVDIMLMLVIFLGLVIVIPFVLIIVSYAIFNLMAISVG (SEQ ID NO: 312)
- 45 TMS - (54) DYAFVFVDIMLHTLVIFLGLVIVIPFVLIIVSYAIFNLMATITVG (SEQ ID NO: 313)

- 32 -

TM5 - (55) CDVAVVYSSDIMLFLVIFLGLVIVIPFVLIIIVSYAIFSSNLCAISSVG (SEQ ID NO: 314)  
 TM5 - (56) CDVFVFDIMLCALMIYILGGLIIIIIPFLLIVMSYVSIFNLCAISVG (SEQ ID NO: 315)  
 TM5 - (57) YAIFVLYDIMLCALMIYILGGLIIIIIPFLLIVMSYVSIFNLCAISVG (SEQ ID NO: 316)  
 TM5 - (58) DYAIFFVFDIMLMTASIFNLMYILGGLIIIIIPFLLIVMSYVLMMAISVG (SEQ ID NO: 317)  
 5 TM5 - (59) DYAIFFVFDIMLHTTASTILMYILGGLIIIIIPFLLIVMSYVITVG (SEQ ID NO: 318)  
 TM5 - (60) CDVAVVYSSDIMLFYVCTAYILGGLIPFLLIVMTYVSIFTNLCAISSVG (SEQ ID NO: 319)  
 TM5 - (61) CDVFVFDIMLCATASIFNLLMIHIMEVIIIVIPFVLIVISYACAIISVG (SEQ ID NO: 320)  
 TM5 - (62) YAIFVLYDIMLCATASIFNLLMIHIMEVIIIVIPFVLIVISYACAIISVG (SEQ ID NO: 321)  
 TM5 - (63) DYAIFFVFDIMLMTASIFLMIHIMEVIIIVIPFVLIVISYAISVG (SEQ ID NO: 322)  
 10 TM5 - (64) DYAIFFVFDIMLHTTASTILMIHIMEVIIIVIPFVLIVISYAITVG (SEQ ID NO: 323)  
 TM5 - (65) CDVAVVYSSDIMLFYVCTASIFLMIHIMEVIIIVIPFVLIVISYAAISVG (SEQ ID NO: 324)

Non-limiting examples of longer consensus GPR polypeptides for domain V across several or many, such as 1-500, or any value or range therein, G-protein receptors are as follows:

15	T	M	1	-	(	1	)	
	TM1NWPALSIVVIIINTIGGNILVIMAVSIYTSLDVMLCTASILNLLISLFVLI GYVCSSSLGINPVIIYTLF (SEQ ID NO: 325)							
	T	M	1	-	(	2	)	
20	NWPALSIVVIIINTIGGNILVIMAVTIYTTLDVMLCTATILNLLISLFVLI GTFVAFFIPLTIMVITYFLFN VCTTTLGINPVIIYTLF (SEQ ID NO: 326)							
	T	M	1	-	(	3	)	
	NWPALTIVVIIINTIGGNILVIMAVSIYTTLDVMLCTATILNLLITLFVLI GTFVAFFIPLTIMVITYFLFN VCSTSLGINPVIIYTLF (SEQ ID NO: 327)							
25	T	M	1	-	(	5	)	
	NWPALTIVVIIINTIGGNILVIMAVTIYTTLDVMLCTATILNLLITLFVLI GTFVAFFIPLTIMVITYFLFN VCTLGINPVIIYTLF (SEQ ID NO: 328)							
	T	M	1	-	(	6	)	
30	NWKNWSALLTVVIILTIAGNILVIMAVSSLDVMLCTASILNLLISLFVLI GSFVAFFIPLTIMVITYFLFN VCSSSLGINPVIIYTLF (SEQ ID NO: 329)							
	T	M	1	-	(	7	)	
	ITITVVLAVLILITVAGNVVVCIAVGSIYTSLDVMLCTASILNLLISLFVLI GSFVAFFIPLTIMVITYFLFN YVCSSSLGINPVIIYTLF (SEQ ID NO: 330)							
35	T	M	1	-	(	8	)	
	TLTLVCIACLSLTVFGNVLVIIAVFSLDVMLCTASILNLLISLFVLI GSFVAFFIPLTIMVITYFLFN SSLGINPVIIYTLF (SEQ ID NO: 331)							
	T	M	1	-	(	9	)	
	TAAIAAAITFLIFTIFGNALVIIAVLSIYTSLDVMLCTASILNLLISLFVLI GSFVAFFIPLTIMVITYFLFN GYVCSSSLGINPVIIYTLF (SEQ ID NO: 332)							
40	T	M	1	-	(	1	0	)
	AISVGLVLGAFILFAIVGNILVILSVANWPALSIVVIIINTIGGNILVIMAV SIYTSLDVMLCTASILNLLISLFVLI GSFVAFFIPLTIMVITYFLFN FVAFFIPLTIMVITYFLFN FVGSYVCSSSLGINPVIIYTLF (SEQ ID NO: 333)							

- 33 -

T	M	1	-	(	1	1	1	)	
AALAGALLALAVLATVGGNLLVIVAIASLDVMLCTASILNLLISLFVLI GSFVAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 334)									
T	M	1	-	(	1	1	2	)	
5	TAGDCLIMLIVLIVAGNVLVIVAIASLDVMLCTASILNLLISLFVLI GSFVAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 335)								
T	M	1	-	(	1	1	3	)	
VITIAVVTAVVSLMTIVGNVLVMSFSIYTS LDVMLCTASILNLLISLFVLI GSFVAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 336)									
10	T	M	1	-	(	1	1	4	)
MVFIATVRGSLSLVTVGNILVMLSISIYTS LDVMLCTASILNLLISLFVLI GSFVAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 337)									
T	M	1	-	(	1	1	5	)	
WFIAFLTGTGILALVTIIGNILVIVSFSIYTS LDVMLCTASILNLLISLFVLI GSFVAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 338)									

Non-limiting examples of longer consensus GPR polypeptides for domain V across several or many, such as 1-500, or any value or range therein, G-protein receptors are as follows:

T	M	3	-	(	1	6	5	)	
20	NWPALSIVVIIINTIGGNILVIMAFFACFVLVLTQSSIFSLLAIA AINLLISLFVLI GSFVAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 339)								
T	M	3	-	(	1	6	6	)	
NWPALSIVVIIINTIGGNILVIMAFFACFVLVLTQSSIFSLLAIA IFVLI GSFVAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 340)									
25	T	M	3	-	(	1	6	7	)
NWPALSIVVIIINTIGGNILVIMAVMVACPV LILTQSSIIALLAIA AVSFVAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 341)									
T	M	3	-	(	1	6	8	)	
NWPALSIVVIIINTIGGNILVIMAVLWLALDY VASNASV LNLLISFFF IPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 342)									
30	T	M	3	-	(	1	6	9	)
NWPALSIVVIIINTIGGNILVIMAVLYVVS NASVMNLLI ISSFVAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 343)									
T	M	3	-	(	1	7	0	)	
35	NWPALSIVVIIINTIGGNILVIMAVLWIA IDYVAS NASV LNLLVISFGSF VAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 344)								
T	M	3	-	(	1	7	1	)	
NWPALSIVVIIINTIGGNILVIMAVLP PFLOKSS VGITV NLCA LSGSF VAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 345)									
40	T	M	3	-	(	1	7	2	)
NWPALSIVVIIINTIGGNILVIMAVC ITYLQYL GINASSCS ITA IIGSF VAFFIPLTIMVITYFLFN VFFVWIGYVCSSSLGINPVI YIYTLF (SEQ ID NO: 346)									

- 34 -

T M 3 ( 1 7 3 )  
NWPALSIVVIIINTIGGNILVIMAVFHNFPIAALFASIYSMTAVAGSFVAFFIPLTIMVITYFLFNFFFVWIGYVCSSS  
LGINPVIIYTLF (SEQ ID NO:347)  
T M 3 ( 1 7 4 )  
5 NWPALSIVVIIINTIGGNILVIMAVIASASFNLVASVFLLTCLSIGSFVAFFIPLTIMVITYFLFNFFFVWIGYVCSSS  
SLGINPVIIYTLF (SEQ ID NO:348)

As another non-limiting, illustrative example of a GPR polypeptide consensus sequences across each individual or different transmembrane domains of 5-HT receptors may be made, such as for 5-HT, as the following:

5HT consensus (4) KNASALLSVIIINSIGGNVVTAVS (SEQ ID NO:349);  
5HT consensus (5) YFLMSLAVTDLVVSFVMPVSAL (SEQ ID NO:350);  
5HT consensus (6) AITKIAITWAISGVSVPFIPVWG (SEQ ID NO:351); and  
15 5HT consensus (7) LGIIFGTFIIIWLPFFITNLVSP (SEQ ID NO:352);

Wherein variations and substitutions of amino acids may be made as described herein.

Alternatively, 5-HT consensus sequences may be provided as consensus peptides of the present invention as consensus peptides for individual transmembrane domains, such as 5-HT domains III, V and VII, e.g., as follows:

5-HT consensus (8): IWISLDVLFSTASSIMHLCAISL (SEQ ID NO:353)  
5-HT consensus (9): GYTIYSTLVTFYIPSVIMVITYG (SEQ ID NO:354)  
5-HT consensus (10): LLNFFNWIGYLNSSLINPVIIYTLF (SEQ ID NO:355)

25 This invention is also directed to an antibody which binds an epitope specific for a GPR polypeptide of the present invention and the use of such an antibody to detect the presence of, or measure the quantity or concentration of, the GPR protein in a cell, a cell or tissue extract, a biological fluid, an extract thereof, a  
30 solution, or sample, *in vitro*, *in situ*, or *in vivo*.

- 35 -

The term "antibody" is meant to include polyclonal antibodies, monoclonal antibodies (mAbs), chimeric antibodies, anti-idiotypic (anti-Id) antibodies to antibodies specific for GPR polypeptide of the present invention, as well as fragments, consensus 5 polypeptides or chemical derivatives thereof.

Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of animals immunized with an antigen.

A monoclonal antibody contains a substantially homogeneous 10 population of antibodies specific to antigens, which population contains substantially similar epitope binding sites. Mabs may be obtained by methods known to those skilled in the art. See, for example Kohler and Milstein, *Nature* 256:495-497 (1975); U.S. Patent No. 4,376,110; Ausubel et al, eds., *Current Protocols in Molecular 15 Biology*, Wiley Interscience, N.Y., (1987, 1992); and Harlow and Lane *Antibodies: A Laboratory Manual* Cold Spring Harbor Laboratory (1988), the contents of which references are incorporated entirely herein by reference. Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, GILD and any subclass thereof. A 20 hybridoma producing a mAb of the present invention may be cultivated *in vitro*, *in situ* or *in vivo*. Production of high titers of mAbs *in vivo* or *in situ* makes this the presently preferred method of production.

Chimeric antibodies are molecules different portions of 25 which are derived from different animal species, such as those having variable region derived from a murine mAb and a human immunoglobulin constant region, which are primarily used to reduce immunogenicity in application and to increase yields in production, for example, where murine mAbs have higher yields from hybridomas but higher 30 immunogenicity in humans, such that human/murine chimeric mAbs are used. Chimeric antibodies and methods for their production are known in the art (Cabilly et al, *Proc. Natl. Acad. Sci. USA* 81:3273-3277 (1984); Morrison et al., *Proc. Natl. Acad. Sci. USA* 81:6851-6855 (1984); Boulian et al., *Nature* 312:643-646 (1984); Cabilly et al., 35 European Patent Application 125023 (published November 14, 1984); Neuberger et al., *Nature* 314:268-270 (1985); Taniguchi et al., European Patent Application 171496 (published February 19, 1985);

Morrison et al., European Patent Application 173494 (published March 5, 1986); Neuberger et al., PCT Application WO 86/01533, (published March 13, 1986); Kudo et al., European Patent Application 184187 (published June 11, 1986); Morrison et al., European Patent Application 173494 (published March 5, 1986); Sahagan et al., J. Immunol. 137:1066-1074 (1986); Robinson et al., International Patent Publication No.PCT/US86/02269 (published 7 May 1987); Liu et al., Proc. Natl. Acad. Sci. USA 84:3439-3443 (1987); Sun et al., Proc. Natl. Acad. Sci. USA 84:214-218 (1987); Better et al., Science 240:1041- 1043 (1988); and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory (1988)). These references are incorporated entirely herein by reference.

An anti-idiotypic (anti-Id) antibody is an antibody which recognizes unique determinants generally associated with the antigen-binding site of an antibody. An Id antibody can be prepared by immunizing an animal of the same species and genetic type (e.g., mouse strain) as the source of the mAb with the mAb to which an anti-Id is being prepared. The immunized animal will recognize and respond to the idotypic determinants of the immunizing antibody by producing an antibody to these idotypic determinants (the anti-Id antibody). See, for example, U.S. patent No. 4,699,880, which is herein entirely incorporated by reference.

The anti-Id antibody may also be used as an "immunogen" to induce an immune response in yet another animal, producing a so-called anti-anti-Id antibody. The anti-anti-Id may be epitopically identical to the original mAb which induced the anti-Id. Thus, by using antibodies to the idotypic determinants of a mAb, it is possible to identify other clones expressing antibodies of identical specificity.

Accordingly, mAbs generated against a GPR polypeptide of the present invention may be used to induce anti-Id antibodies in suitable animals, such as BALB/c mice. Spleen cells from such immunized mice are used to produce anti-Id hybridomas secreting anti-Id mAbs. Further, the anti-Id mAbs can be coupled to a immunogenic carrier such as keyhole limpet hemocyanin (KLH) or cationized bovine serum albumin and used to immunize additional BALB/c mice. Sera from these mice will contain anti-anti-Id antibodies that have the binding

- 37 -

properties of the original mAb specific for a GPR polypeptide epitope.

The anti-Id mAbs thus have their own idiotypic epitopes, or "idiotypes" structurally similar to the epitope being evaluated.

5       The term "antibody" is also meant to include both intact molecules as well as fragments thereof, such as, for example, Fab and F(ab')<sub>2</sub>, which are capable of binding antigen. Fab and F(ab')<sub>2</sub> fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding  
10 than an intact antibody (Wahl et al., J. Nucl. Med. 24:316-325 (1983)).

15      It will be appreciated that Fab and F(ab')<sub>2</sub>, and other fragments of the antibodies useful in the present invention may be used for the detection and quantitation of a GPR polypeptide according to the methods disclosed herein for intact antibody molecules. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments).

20      An antibody is said to be "capable of binding" a molecule if it is capable of specifically reacting with the molecule to thereby bind the molecule to the antibody. The term "epitope" is meant to refer to that portion of any molecule capable of being bound by an antibody which can also be recognized by that antibody. Epitopes or "antigenic determinants" usually consist of chemically  
25 active surface groupings of molecules such as amino acids, lipids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics.

30      An "antigen" is a molecule or a portion of a molecule capable of being bound by an antibody which is additionally capable of inducing an animal to produce antibody capable of binding to an epitope of that antigen. An antigen may have one, or more than one epitope. The specific reaction referred to above is meant to indicate that the antigen will react, in a highly selective manner, with its corresponding antibody and not with the multitude of other  
35 antibodies which may be evoked by other antigens.

The antibodies, or fragments of antibodies, useful in the present invention may be used to quantitatively or qualitatively

detect a GPR polypeptide in a sample or to detect presence of cells which express a GPR polypeptide of the present invention. This can be accomplished by immunofluorescence techniques employing a fluorescently labeled antibody (see below) coupled with light 5 microscopic, flow cytometric, or fluorometric detection.

The antibodies (of fragments thereof) useful in the present invention may be employed histologically, as in immunofluorescence or immunoelectron microscopy, for *in situ* detection of a GPR polypeptide of the present invention. *In situ* detection may be 10 accomplished by removing a histological specimen from a patient, and providing the a labeled antibody of the present invention to such a specimen. The antibody (or fragment) is preferably provided by applying or by overlaying the labeled antibody (or fragment) to a biological sample. Through the use of such a procedure, it is 15 possible to determine not only the presence of a GPR polypeptide but also its distribution on the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of wide variety of histological methods (such as staining procedures) can be modified in order to achieve such *in situ* detection.

Such assays for a GPR polypeptide of the present invention typically comprise incubating a biological sample, such as a biological fluid, a tissue extract, freshly harvested cells such as lymphocytes or leukocytes, or cells which have been incubated in tissue culture, in the presence of a detectably labeled antibody 20 capable of identifying a GPR polypeptide, and detecting the antibody by any of a number of techniques well-known in the art. See, e.g., Harlow and Lane, supra; Ausubel et al, supra; and Sambrook et al, supra.

The biological sample may be treated with a solid phase 25 support or carrier, such as nitrocellulose, or other solid support or carrier which is capable of immobilizing cells, cell particles or soluble proteins. The support or carrier may then be washed with suitable buffers, followed by treatment with a detectably labeled GPR polypeptide-specific antibody. The solid phase support or carrier 30 may then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on said solid support or carrier

- 39 -

may then be detected by known method steps, see, e.g., Harlow, supra; Ausubel, supra; or Sambrook, supra.

By "solid phase support", "solid phase carrier", "solid support", "solid carrier", "support" or "carrier" is intended any support or carrier capable of binding antigen or antibodies. Well-known supports or carriers, include glass, polystyrene, polypropylene, polyethylene, dextran, nylon amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support or carrier configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, polymer test strip, etc. Preferred supports or carriers include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

The binding activity of a given lot of anti-GPR polypeptide antibody may be determined according to well known method steps. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation. See, e.g., Harlow, supra.

Other such steps as washing, stirring, shaking, filtering and the like may be added to the assays as is customary or necessary for the particular situation.

One of the ways in which a GPR polypeptide-specific antibody, anti-idiotype antibody or fragment thereof, can be detectably labeled is by linking the same to an enzyme and use in an enzyme immunoassay (EIA). This enzyme, in turn, when later exposed to an appropriate substrate, will react with the substrate in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorometric or by visual means. Enzymes which can be used detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease,

- 40 -

delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-5-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. The detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared 10 standards. See, Harlow, supra, Ausubel, supra.

Detection may be accomplished using any of a variety of other immunoassays. For example, by radioactivity labeling the antibodies or antibody fragments, it is possible to detect R-PTPase through the use of a radioimmunoassay (RIA). A good description of 15 RIA maybe found in *Laboratory Techniques and Biochemistry in Molecular Biology*, by Work et al., North Holland Publishing Company, NY (1978) with particular reference to the chapter entitled "An Introduction to Radioimmune Assay and Related Techniques" by Chard, incorporated entirely by reference herein. The radioactive isotope 20 can be detected by such means as the use of a  $\gamma$ -counter, a scintillation counter or by autoradiography.

It is also possible to label an anti-GPR polypeptide antibody, anti-idiotype antibody or fragment thereof, with a fluorescent compound. When the fluorescently labeled antibody is 25 exposed to light of the proper wave length, its presence can be then be detected due to fluorescence. Among the most commonly used fluorescent labelling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine, commercially available, e.g., from 30 Molecular Probes, Inc. (Eugene, Ore.).

The antibody can also be detectably labeled using fluorescence emitting metals such as  $^{152}\text{Eu}$ , or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriamine pentaacetic 35 acid (EDTA).

The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the

- 41 -

chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester,  
5 imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in which a catalytic protein increases the efficiency of the chemiluminescent reaction.  
10 The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

An antibody molecule of the present invention may be adapted for utilization in a immunometric assay, also known as a  
15 "two-site" or "sandwich" assay. In a typical immunometric assay, a quantity of unlabeled antibody (or fragment of antibody) is bound to a solid support or carrier and a quantity of detectably labeled soluble antibody is added to permit detection and/or quantitation of the ternary complex formed between solid-phase antibody, antigen, and  
20 labeled antibody.

Typical, and preferred, immunometric assays include "forward" assays in which the antibody bound to the solid phase is first contacted with the sample being tested to extract the antigen from the sample by formation of a binary solid phase antibody-antigen  
25 complex. After a suitable incubation period, the solid support or carrier is washed to remove the residue of the fluid sample, including unreacted antigen, if any, and then contacted with the solution containing an unknown quantity of labeled antibody (which functions as a "reporter molecule"). After a second incubation  
30 period to permit the labeled antibody to complex with the antigen bound to the solid support or carrier through the unlabeled antibody, the solid support or carrier is washed a second time to remove the unreacted labeled antibody.

In another type of "sandwich" assay, which ~~may also be~~  
35 useful with the antigens of the present invention, the so-called "simultaneous" and "reverse" assays are used. A "simultaneous" and "reverse" assays are used. A simultaneous assay involves a single

- 42 -

incubation step as the antibody bound to the solid support or carrier and labeled antibody are both added to the sample being tested at the same time. After the incubation is completed, the solid support or carrier is washed to remove the residue of fluid sample and  
5 uncomplexed labeled antibody. The presence of labeled antibody associated with the solid support or carrier is then determined as it would be in a conventional "forward" sandwich assay.

In the "reverse" assay, stepwise addition first of a solution of labeled antibody to the fluid sample followed by the  
10 addition of unlabeled antibody bound to a solid support or carrier after a suitable incubation period is utilized. After a second incubation, the solid phase is washed in conventional fashion to free it of the residue of the sample being tested and the solution of unreacted labeled antibody. The determination of labeled antibody  
15 associated with a solid support or carrier is then determined as in the "simultaneous" and "forward" assays. See, e.g., for the above-mentioned immunological techniques, Harlow, supra; Ausubel et al, supra; and Sambrook et al, supra. GPR polypeptides of the present invention can be made by chemical synthesis or by recombinant  
20 methods, wherein chemical synthesis is preferred.

Synthetic production of transmembrane proteins of the present invention

GPR polypeptides, variants and chemical derivatives thereof can be synthesized according to known method steps, including  
25 portions of known GPR transmembrane domains, consensus peptides thereof, conservative substitution derivative thereof or functional derivatives thereof.

Chemical polypeptide synthesis is a rapidly evolving area in the art, and methods of solid phase polypeptide synthesis are  
30 well-described in the following references, hereby entirely incorporated by reference: (Merrifield, B., J. Amer. Chem. Soc. 85:2149-2154 (1963); Merrifield, B., Science 232:341-347 (1986); Wade, J.D. et al., Biopolymers 25:S21-S37 (1986); Fields, G.B., Int. J. Polypeptide Prot. Res. 35:161 (1990); MilliGen Report Nos. 2 and  
35 2a, Millipore Corporation, Bedford, MA, 1987) Ausubel et al, supra, and Sambrook et al. supra.

- 43 -

In general, as is known in the art, such methods involve blocking or protecting reactive functional groups, such as free amino, carboxyl and thio groups. After polypeptide bond formation, the protective groups are removed (or de-protected). Thus, the 5 addition of each amino acid residue requires several reaction steps for protecting and deprotecting. Current methods utilize solid phase synthesis, wherein the C-terminal amino acid is covalently linked to an insoluble resin particle large enough to be separated from the fluid phase by filtration. Thus, reactants are removed by washing 10 the resin particles with appropriate solvents using an automated programmed machine. The completed polypeptide chain is cleaved from the resin by a reaction which does not affect polypeptide bonds.

In the more classical method, known as the "tBoc method," the amino group of the amino acid being added to the resin-bound 15 C-terminal amino acid is blocked with tert-butyloxycarbonyl chloride (tBoc). This protected amino acid is reacted with the bound amino acid in the presence of the condensing agent dicyclohexylcarbodiimide, allowing its carboxyl group to form a polypeptide bond the free amino group of the bound amino acid. The 20 amino-blocking group is then removed by acidification with trifluoroacetic acid (TFA); it subsequently decomposes into gaseous carbon dioxide and isobutylene. These steps are repeated cyclically for each additional amino acid residue. A more vigorous treatment with hydrogen fluoride (HF) or trifluoromethanesulfonyl derivatives 25 is common at the end of the synthesis to cleave the benzyl-derived side chain protecting groups and the polypeptide-resin bond.

More recently, the preferred "Fmoc" technique has been introduced as an alternative synthetic approach, offering milder reaction conditions, simpler activation procedures and compatibility 30 with continuous flow techniques. This method was used, e.g., to prepare the peptide sequences disclosed in the present application. Here, the  $\alpha$ -amino group is protected by the base labile 9-fluorenylmethoxycarbonyl (Fmoc) group. The benzyl side chain protecting groups are replaced by the more acid labile t-butyl 35 derivatives. Repetitive acid treatments are replaced by deprotection with mild base solutions, e.g., 20% piperidine in dimethylformamide (DMF), and the final HF cleavage treatment is eliminated. A TFA

- 44 -

solution is used instead to cleave side chain protecting groups and the polypeptide resin linkage simultaneously.

At least three different polypeptide-resin linkage agents can be used: substituted benzyl alcohol derivatives that can be 5 cleaved with 95% TFA to produce a polypeptide acid, methanolic ammonia to produce a polypeptide amide, or 1% TFA to produce a protected polypeptide which can then be used in fragment condensation procedures, as described by Atherton, E. et al., *J. Chem. Soc. Perkin Trans. 1*:538-546 (1981) and Sheppard, R.C. et al., *Int. J. Polypeptide Prot. Res.* 20:451-454 (1982). Furthermore, highly 10 reactive Fmoc amino acids are available as pentafluorophenyl esters or dihydro-oxobenzotriazine esters derivatives, saving the step of activation used in the tBoc method.

Sequences available to use as a basis for polypeptide 15 synthesis can be based on published sequences of G-protein coupled receptors, ligands and/or effectors, wherein the transmembrane or functional domains correspond to sections of hydrophobic or other amino acids of 5 to 100 amino acids, such as 5-10, 10-15, 15-25, 20-25, 23-27, 25-30, 28-35, 20-40, 10-40, 20-30, 30-40, 40-50, 10-80, 20 20-60 or 25-40 amino acids in length. Recombinant production of GPR polypeptides can be accomplished according to known method steps. Standard reference works setting forth the general principles of recombinant DNA technology include Watson, J.D. et al., *Molecular Biology of the Gene*, Volumes I and II, The Benjamin/Cummings 25 Publishing Company, Inc., publisher, Menlo Park, CA (1987); Darnell, J.E. et al., *Molecular Cell Biology*, Scientific American Books, Inc., publisher, New York, NY (1986); Lewin, B.M., *Genes III*, John Wiley & Sons, publishers, New York, NY (1989); Old, R.W., et al., *Principles of Gene Manipulation: An Introduction to Genetic 30 Engineering*, 2d edition, University of California Press, publisher, Berkeley, CA (1981); Ausubel et al, eds., *Current Protocols in Molecular Biology*, Wiley Interscience, publisher, New York, NY (1987, 1992); and Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory, publisher, Cold 35 Spring Harbor, NY (1989), the entire contents of which references are herein incorporated by reference.

A nucleic acid sequence encoding a GPR polypeptide of the present invention may be recombined with vector DNA in accordance with conventional techniques, including blunt-ended or staggered-ended termini for ligation, restriction enzyme digestion 5 to provide appropriate termini, filling in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and ligation with appropriate ligases. Techniques for such manipulations are disclosed, e.g., by Ausubel et al, *supra*, and are well known in the art.

10 A nucleic acid molecule, such as DNA, is said to be "capable of expressing" a polypeptide if it contains nucleotide sequences which contain transcriptional and translational regulatory information and such sequences are "operably linked" to nucleotide sequences which encode the polypeptide. An operable linkage is a 15 linkage in which the regulatory DNA sequences and the DNA sequence sought to be expressed are connected in such a way as to permit gene expression as GPR polypeptides in recoverable amounts. The precise nature of the regulatory regions needed for gene expression may vary from organism to organism, as is well known in the analogous art.

20 See, e.g., Sambrook, *supra* and Ausubel *supra*.

The present invention accordingly encompasses the expression of a GPR polypeptide, in either prokaryotic or eukaryotic cells, although eukaryotic expression is preferred.

Preferred hosts are bacterial or eukaryotic hosts including 25 bacteria, yeast, insects, fungi, bird and mammalian cells either *in vivo*, or *in situ*, or host cells of mammalian, insect, bird or yeast origin. It is preferred that the mammalian cell or tissue is of human, primate, hamster, rabbit, rodent, cow, pig, sheep, horse, goat, dog or cat origin, but any other mammalian cell may be used.

30 Further, by use of, for example, the yeast ubiquitin hydrolase system, *in vivo* synthesis of ubiquitin-transmembrane polypeptide fusion proteins may be accomplished. The fusion proteins so produced may be processed *in vivo* or purified and processed *in vitro*, allowing synthesis of a GPR polypeptide of the present 35 invention with a specified amino terminus sequence. Moreover, problems associated with retention of initiation codon-derived methionine residues in direct yeast (or bacterial) expression may be

avoided. Sabin et al., *Bio/Technol.* 7(7): 705-709 (1989); Miller et al., *Bio/Technol.* 7(7): 698-704 (1989).

Any of a series of yeast gene expression systems incorporating promoter and termination elements from the actively expressed genes coding for glycolytic enzymes produced in large quantities when yeast are grown in mediums rich in glucose can be utilized to obtain GPR polypeptides of the present invention. Known glycolytic genes can also provide very efficient transcriptional control signals. For example, the promoter and terminator signals of the phosphoglycerate kinase gene can be utilized.

Production of GPR polypeptides or functional derivatives thereof in insects can be achieved, for example, by infecting the insect host with a baculovirus engineered to express transmembrane polypeptide by methods known to those of skill. See Ausubel et al, eds. *Current Protocols in Molecular Biology*, Wiley Interscience, §§16.8-16.11 (1987, 1992).

In a preferred embodiment, the introduced nucleotide sequence will be incorporated into a plasmid or viral vector capable of autonomous replication in the recipient host. Any of a wide variety of vectors may be employed for this purpose. See, e.g., Ausubel et al, *supra*, §§ 1.5, 1.10, 7.1, 7.3, 8.1, 9.6, 9.7, 13.4, 16.2, 16.6, and 16.8-16.11. Factors of importance in selecting a particular plasmid or viral vector include: the ease with which recipient cells that contain the vector may be recognized and selected from those recipient cells which do not contain the vector; the number of copies of the vector which are desired in a particular host; and whether it is desirable to be able to "shuttle" the vector between host cells of different species.

Preferred prokaryotic vectors known in the art include plasmids such as those capable of replication in *E. coli* (such as, for example, pBR322, ColE1, pSC101, pACYC 184,  $\pi$ VX). Such plasmids are, for example, disclosed by Maniatis, T., et al. (*Molecular Cloning, A Laboratory Manual*, Second Edition, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989); Ausubel et al, eds., *Current Protocols in Molecular Biology*, Wiley Interscience, New York, NY (1987, 1992)). *Bacillus* plasmids include pC194, pC221, pT127, etc. Such plasmids are disclosed by Gryczan, T. (In: *The Molecular*

- 47 -

Biology of the Bacilli, Academic Press, NY (1982), pp. 307-329). Suitable Streptomyces plasmids include pIJ101 (Kendall, K.J., et al., J. Bacteriol. 169:4177-4183 (1987)), and streptomyces bacteriophages such as φC31 (Chater, K.F., et al., In: Sixth International 5 Symposium on Actinomycetales Biology, Akademiai Kaido, Budapest, Hungary (1986), pp. 45-54). Pseudomonas plasmids are reviewed by John, J.F., et al. (Rev. Infect. Dis. 8:693-704 (1986)), and Izaki, K. (Jpn. J. Bacteriol. 33:729-742 (1978); and Ausubel et al, supra).

The expressed protein may be isolated and purified in 10 accordance with conventional conditions, such as extraction, precipitation, chromatography, affinity chromatography, electrophoresis, or the like. For example, the cells may be collected by centrifugation, or with suitable buffers, lysed, and the protein isolated by column chromatography, for example, on 15 DEAE-cellulose, phosphocellulose, polyribocytidylic acid-agarose, hydroxyapatite or by electrophoresis or immunoprecipitation. Alternatively, the transmembrane polypeptide or functional derivative thereof may be isolated by the use of anti-transmembrane polypeptide antibodies. Such antibodies may be obtained by well-known methods, 20 some of which are mentioned below. These antibodies may be immobilized on cellulose, agarose, hollow fibers, or cellulose filters by covalent chemical derivatives by methods well known to those skilled in the art.

As discussed herein, GPR polypeptides of the present 25 invention may be further modified for purposes of drug design, such as for example to reduce immunogenicity, to prevent solubility and/or enhance delivery, or to prevent clearance or degradation.

Appropriate modification of the primary amino acid sequence of GPR polypeptides of the present invention, obtained by mutagenesis 30 or utilizing fragments of other related forms of G-protein transmembrane proteins, as described herein, will allow the creation of molecules which bind G-protein coupled receptors with higher affinity than that exhibited by naturally occurring transmembrane domains. Small polypeptides that are provided according to the 35 present invention which polypeptides maintain G-protein coupled receptor binding inhibition activity, are expected to have two

- 48 -

advantages over larger polypeptides. These advantages include (1) greater stability and diffusibility, and (2) less immunogenicity.

Since polypeptides according to the present invention are generally small (10-40, 20-30, 15-25, 30-45 amino acids), cell or tissue sources of G-protein coupled receptors are not required to practice the present invention, since known polypeptide syntheses steps can be used without undue experimentation to provide GPR polypeptides or sequences substantially corresponding thereto.

Pharmaceutical Preparations

10 Preparations of GPR polypeptides for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions, which may contain auxiliary agents or excipients which are known in the art. Pharmaceutical compositions such as tablets and capsules can also be prepared according to 15 routine methods.

By the term "protection" from infection or disease as used herein is intended "prevention," "suppression" or "treatment." "Prevention" involves administration of a GPR polypeptide, polypeptide derivative, or anti-idiotypic antibody prior to the 20 induction of the disease.

"Suppression" involves administration of the composition prior to the clinical appearance of the disease.

"Treatment" involves administration of the protective composition after the appearance of the disease. It will be 25 understood that in human and veterinary medicine, it is not always possible to distinguish between "preventing" and "suppressing" since the ultimate inductive event or events may be unknown, latent, or the patient is not ascertained until well after the occurrence of the event or events. Therefore, it is common to use the term 30 "prophylaxis" as distinct from "treatment" to encompass both "preventing" and "suppressing" as defined herein. The term "protection," as used herein, is meant to include "prophylaxis."

At least one GPR polypeptide, antibody or anti-idiotypic antibody of the present invention may be administered by any means 35 that achieve their intended purpose, for example, to treat GPR related pathologies, such as psychotic disorders, including schizophrenia, by inhibition of binding of Dopamine D<sub>2</sub> receptors

- 49 -

using a GPR polypeptide corresponding to a fragment or consensus portion of a dopamine D<sub>2</sub> transmembrane domain; in the form of a pharmaceutical composition.

For example, administration of such a composition may be by 5 various parenteral routes such as subcutaneous, intravenous, intradermal, intramuscular, intraperitoneal, intranasal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. Parenteral administration can be by bolus injection or by gradual perfusion over time.

10 A preferred mode of using a GPR pharmaceutical composition of the present invention is by intravenous or parenteral application.

A typical regimen for preventing, suppressing, or treating G-protein coupled receptor pathologies, such as dopamine receptor related schizophrenia, comprises administration of an effective 15 amount of a GPR polypeptide, consensus sequence, or chemical derivative thereof, administered over a period of one or several days, up to and including between one week and about 24 months.

It is understood that the dosage of a GPR polypeptide of the present invention administered *in vivo* or *in vitro* will be 20 dependent upon the age, sex, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. The ranges of effective doses provided below are not intended to limit the inventors and represent preferred dose ranges. However, the most preferred dosage will be tailored to 25 the individual subject, as is understood and determinable by one of skill in the art, without undue experimentation.

The total dose required for each treatment may be administered by multiple doses or in a single dose. a GPR polypeptide or functional a chemical derivative thereof may be 30 administered alone or in conjunction with other therapeutics directed to GPR related pathologies, such as a the dopamine receptor related pathology as a non limiting example, or directed to other symptoms of the disease.

---

35 Effective amounts of the a GPR polypeptide or composition, which may also include a functional derivative thereof, or a GPR anti-idiotypic antibody, are from about 0.01 µg to about 100 mg/kg body weight, and preferably from about 10 µg to about 50 mg/kg body

- 50 -

weight, such 0.05, 0.07, 0.09, 0.1, 0.5, 0.7, 0.9, 1, 2, 5, 10, 20, 25, 30, 40, 45, or 50 mg/kg.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions, which 5 may contain auxiliary agents or excipients which are known in the art. Pharmaceutical compositions such as tablets and capsules can also be prepared according to routine methods.

Pharmaceutical compositions comprising at least one GPR polypeptide of the present invention may 10 include all compositions wherein the GPR polypeptide is contained in an amount effective to achieve its intended purpose. In addition to the GPR polypeptide, a pharmaceutical composition may contain suitable pharmaceutically acceptable carriers, such as comprising excipients and auxiliaries which facilitate processing of the active 15 compounds into preparations which can be used pharmaceutically.

Pharmaceutical compositions include suitable solutions for administration intravenously, subcutaneously, dermally, orally, mucosally, rectally or by injection or orally, and contain from about 0.01 to 99 percent, preferably from about 20 to 75 percent of 20 active component (i.e. the antibody) together with the excipient. Pharmaceutical compositions for oral administration include tablets and capsules. Compositions which can be administered rectally include suppositories.

Example 1: Synthesis of a G-Protein Transmembrane Polypeptide and  
25 Consensus Polypeptide

The polypeptides in Figs. 1-5 were synthesized using the following procedure and include the following characteristics.

Peptide I (SEQ ID NO:1), as shown in Fig. 1, was used as a control for hydrophobic interaction alone as the mechanism of binding 30 and was run in parallel with the test polypeptides described below. Polypeptide II (SEQ ID NO:2), as shown in Fig. 2, represents a membrane-spanning fragment of transmembrane segment III in the dopamine D<sub>1</sub> receptor. This particular fragment was chosen since it has been implicated in the β-adrenergic receptor as having many 35 residues which are involved in ligand binding interaction.

- 51 -

Polypeptide III (SEQ ID NO:3), as shown in Fig. 3, represents the consensus polypeptide which was developed as a model for the dopamine D<sub>2</sub> system and polypeptide IV (SEQ ID NO:4), as shown in Fig. 4, is a control for length dependence to show how critical the polypeptide 5 length is in binding studies. Polypeptide V (SEQ ID NO:5), as shown in Fig. 5, is a consensus sequence of transmembrane domains of dopamine receptors D<sub>1</sub> and D<sub>2</sub>.

The above polypeptides I-V (SEQ ID NOS:1-5), as shown in Figs. 1-5, respectively, were synthesized using solid phase synthesis 10 on a Milligen 9600 polypeptide synthesizer using Fmoc amino acids (provided by Milligen/Bioscience) and PAL polystyrene resin (Milligen/Bioscience). Coupling times were 1 hour and the polypeptides were cleaved by trifluoroacetic acid/phenol/H<sub>2</sub>O/thioanisole/ethanedithiol (82.5:5:5:5:2.5) at room 15 temperature for 2 hours. The filtrate was collected and washed with 2 mL of trifluoroacetic acid (TFA) and 1 mL of dichloromethane (DCM). The filtrate was reduced in vacuo to 2 ml in volume and the resulting polypeptide was precipitated out by the addition of water. The polypeptides were then dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol 20 [(HFIP) Eastman]; lyophilized; and stored at -20°C until purification. Polypeptides I-V (SEQ ID NOS:1-5), were purified using reverse-phase HPLC using a preparative Vydac C4 column (Vydac) at 60°C at a flow rate of 6.0 mL/min with a linear gradient of 0-100% B in a 60 min period at a UV detection wavelength of 275 nm.

25 Due to the highly hydrophobic nature of these polypeptides, methanol was used with 0.1% (W/V) TFA and 0.5% (W/V) HFIP as solvent A and 2-propanol with 0.1% TFA as solvent B, in order to purify these polypeptides. Further purification was performed with an analytical C4 column (Vydac) with an isocratic gradient of 40% B at a flow rate 30 of 1 ml/min. Identity of the polypeptides was confirmed by Fast-atom bombardment mass spectrometry and electrospray mass spectrometry and amino acid analysis. Stock solutions of polypeptides were made in HFIP and stored at -20°- 80°C.

---

35 Circular Dichroism (CD). Spectra were recorded on an Aviv model 60 DS circular dichroism spectrophotometer at room temperature with a 1 cm by 1 mm cell. The amplitude of the CD signal was calibrated using 1 0.1% (w/v) solution of d (+)-camphorsulfonic acid

- 52 -

(Aldrich) and the wavelength of the CD signal was set using standard absorbance peaks of benzene vapor. Polypeptide concentrations were determined in a Cary 210 UV spectrophotometer with the absorbance measured at 280 nm. Helical content was estimated using CD signal intensity according to the method of Chen. et al Biochem. 13:3350-3359 (1974). This calculation compares the experimental ellipticity at 222 nm ( $[\theta]_{222}$ ) ( $[\theta]$ ) to a theoretical  $[\theta]_{222}$ . The theoretical  $[\theta]_{222}$  is empirically adjusted to account for differences in polypeptide length and is based on experimental CD data from a series of proteins with known crystal structures. Since both the curve shape and magnitude are important in analysis of a CD spectrum for secondary structure contributions, we also considered qualitatively the contributions to the spectral shapes from different secondary structures using reference curves for poly (L-lysine).

Fig. 6 shows a CD spectrum of the consensus polypeptide III (SEQ ID NO:3) demonstrating that the polypeptide III is only partially helical in a solvent system in which most membrane polypeptides are strongly helical.

Preparation of Small Unilamellar Vesicles. Polypeptides were incorporated into DMPC vesicles at lipid:peptide ratio of 147:1 in the following manner: polypeptide in HFIP was mixed with dimyristoyl-phosphatidylcholine (synthetic) (DMPC) in dry chloroform and dried to a film with a stream of dry nitrogen at 0°C. This residue was then dried further overnight under a vacuum ( $1 \times 10^{-2}$  torr). The residue was then hydrated in 100 mM NaCl and sonicated for a 30-min period under nitrogen at 0°C. The suspension was sedimented for a 30-min at 100,000 g (4°C) to remove any residual titanium particles and large unilamellar vesicles. The supernatant was removed and sedimented once more at 159,000 g for a 45 min period at 4°C. The supernatant in the lower portion was used immediately. This basic procedure has been shown to reliably produce small unilamellar vesicles.

Radioligand Binding Assays. A 0.50 mL volume of 1.00 nM [<sup>3</sup>H]-spiperone (New England specific activity 21.4 Ci/mmol) was added to assay tubes which contained 0.5 mL lipid/peptide supernatant, 0.5 mL Tris buffer pH 7.4 and 0.5 mL of cold drug for a final volume of 2.0 mL. Nonspecific binding was defined in the presence of 1 uM of

(+) butaclamol or 1 uM spiperone. Appropriate controls for lipid vesicles containing no polypeptide were also run. Assay tubes were prepared in triplicate and the mixture was incubated for 1 h at 25°C. Incubation was terminated by filtration through filters presoaked in 5 0.1% polyethyleneimine (w/v, Sigma) for at least 1 h prior to use.

Filters were then washed with 6.0 mL of cold 50 mM Tris-HCl buffer, pH 7.40. For detection of radioactivity, filters were placed in 2.0 mL of scintillation fluid (Scintiverse) and incubated for 24 h. The activity of the tritium was determined in a Beckman LS 7500 10 liquid scintillation counter. Specific binding of [<sup>3</sup>H]-spiperone was defined as the difference in binding in the presence and absence of unlabeled (+) butaclamol.

Fig. 7 shows results of radioligand binding assays comparing polypeptide I (SEQ ID NO:1) as a control unit polypeptide 15 III (SEQ ID NO:3) according to the present invention. Polypeptide III (SEQ ID NO:3) is shown to unexpectedly provide receptor-like functional binding, as demonstrated by binding to the neuroleptic agent, spiperone, into a stereoselective, concentration-dependent manner.

20 It has also been demonstrated that as little as 0.1% of a GPR polypeptide according to the present invention is able to form a receptor-like functional binding site. Thus, a GPR polypeptide of the present invention is unexpectedly shown to act both as GPR ligands and GPR binding sites.

25 All references cited herein, including journal articles or abstracts, published or corresponding U.S. or foreign patent applications, issued U.S. or foreign patents, or any other references, are entirely incorporated by reference herein, including all data, tables, figures, and text presented in the cited 30 references. Additionally, the contents of the references cited within the references cited herein are also entirely incorporated by reference.

Reference to known method steps, conventional methods  
steps, known methods or conventional methods is not in any way an  
admission that any aspect, description or embodiment of the present  
35 invention is disclosed, taught or suggested in the relevant art.

- 54 -

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art (including the contents of the references cited herein), readily modify and/or adapt 5 for various applications such specific embodiments, without undue experimentation, without departing from the generic concept of the present invention. Therefore, such adaptations and modifications are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and 10 guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance presented herein.

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

- (i) APPLICANT: Murphy, Randall B.  
Schuster, David I.
- 5 (ii) TITLE OF INVENTION: POLYPEPTIDES OF G-COUPLED RECEPTOR PROTEINS, AND  
COMPOSITIONS AND METHODS THEREOF
- (iii) NUMBER OF SEQUENCES: 95
- 10 (iv) CORRESPONDENCE ADDRESS:  
(A) ADDRESSEE: BROWDY AND NEIMARK  
(B) STREET: 419 Seventh Street, N.W.  
(C) CITY: Washington  
(D) STATE: D.C.  
(E) COUNTRY: USA  
(F) ZIP: 20004
- 15 (v) COMPUTER READABLE FORM:  
(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25
- 20 (vi) CURRENT APPLICATION DATA:  
(A) APPLICATION NUMBER: US 07/943,236  
(B) FILING DATE: 10-SEP-1992  
(C) CLASSIFICATION:
- 25 (viii) ATTORNEY/AGENT INFORMATION:  
(A) NAME: Townsend, Kevin G.  
(B) REGISTRATION NUMBER: 34,033  
(C) REFERENCE/DOCKET NUMBER: MURPHY=2
- (ix) TELECOMMUNICATION INFORMATION:  
(A) TELEPHONE: 202-628-5197  
30 (B) TELEFAX: 202-737-3528  
(C) TELEX: 248633

## (2) INFORMATION FOR SEQ ID NO:1:

- 35 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 24 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:  
40 Leu Ser Leu Leu Leu Ser Leu Leu Ser Leu Leu Ser  
1 5 10 15
- Leu Leu Leu Ser Leu Tyr Tyr Tyr  
20

## (2) INFORMATION FOR SEQ ID NO:2:

- 45 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 27 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear
- 50 (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:  
Asp Asp Ile Phe Val Thr Leu Asp Val Leu Phe Ser Thr Ala Ser Ile  
1 5 10 15
- Leu Asn Leu Ser Ala Ile Ser Leu Lys Lys Lys  
55 20 25

- 56 -

- (2) INFORMATION FOR SEQ ID NO:3:
- 5           (i) SEQUENCE CHARACTERISTICS:  
              (A) LENGTH: 26 amino acids  
              (B) TYPE: amino acid  
              (C) STRANDEDNESS: single  
              (D) TOPOLOGY: linear  
         (ii) MOLECULE TYPE: peptide
- 10           (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:  
             Asp Tyr Ala Ile Phe Val Leu Tyr Ala Ser Ala Trp Leu Ser Phe Asn  
             1               5               10               15
- Cys Pro Phe Ile Val Thr Leu Asn Ile Lys  
             20               25
- 15           (2) INFORMATION FOR SEQ ID NO:4:
- 15           (i) SEQUENCE CHARACTERISTICS:  
              (A) LENGTH: 16 amino acids  
              (B) TYPE: amino acid  
              (C) STRANDEDNESS: single  
              (D) TOPOLOGY: linear  
         (ii) MOLECULE TYPE: peptide
- 20           (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:  
             Lys Ala Val Val Tyr Ser Ser Ile Val Ser Phe Tyr Val Phe Ile Asp  
             1               5               10               15
- 25           (2) INFORMATION FOR SEQ ID NO:5:
- 25           (i) SEQUENCE CHARACTERISTICS:  
              (A) LENGTH: 27 amino acids  
              (B) TYPE: amino acid  
              (C) STRANDEDNESS: single  
              (D) TOPOLOGY: linear  
         (ii) MOLECULE TYPE: peptide
- 30           (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:  
             Asp Cys Asp Val Phe Val Phe Val Asp Ile Met Leu Cys Thr Ala Ser  
             1               5               10               15
- Ile Phe Asn Leu Cys Ala Ile Ser Val Gly Lys  
             20               25
- 35           (2) INFORMATION FOR SEQ ID NO:6:
- 35           (i) SEQUENCE CHARACTERISTICS:  
              (A) LENGTH: 317 amino acids  
              (B) TYPE: amino acid  
              (C) STRANDEDNESS: single  
              (D) TOPOLOGY: linear  
         (ii) MOLECULE TYPE: peptide
- 40           (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:  
             Ser Leu Val Leu Leu Leu Phe Ala Asp Phe Ser Ser Met Leu Gly Cys  
             1               5               10               15
- 45           Met Ala Val Leu Ile Gly Phe Trp Arg Leu Lys Leu Leu Arg Asn His  
             20               25               30
- Val Thr Lys Val Ile Ala Cys Phe Cys Ala Thr Ser Phe Cys Lys Asp  
             35               40               45
- 50           Phe Pro Ser Thr Ile Leu Thr Leu Thr Asn Thr Ala Val Asn Gly Gly  
             50               55               60
- Phe Pro Cys Tyr Leu Tyr Ala Ile Val Ile Thr Tyr Gly Ser Phe Ala  
             65               70               75               80

- 57 -

	Cys Trp Leu Trp Thr Leu Ile Cys Leu Ala Ile Ser Ile Tyr Met Leu	
	85 90 95	
	Ile Val Lys Arg Glu Pro Glu Pro Glu Leu Phe Glu Lys Tyr Tyr Tyr	
	100 105 110	
5	Leu Leu Cys Trp Gly Leu Pro Leu Ile Ser Thr Ile Gly Leu Lys Asn	
	115 120 125	
	Thr Val Gln Phe Val Gly Asn Trp Cys Trp Ile Gly Val Ser Phe Thr	
	130 135 140	
10	Gly Tyr Arg Phe Gly Leu Phe Tyr Pro Phe Leu Phe Ile Trp Ala Ile	
	145 150 155 160	
	Ser Ala Val Leu Val Gly Leu Thr Ser Arg Tyr Thr Tyr Trp Ile His	
	165 170 175	
	Asn Gly Val Ser Asp Asn Lys Glu Lys His Leu Thr Tyr Gln Phe Lys	
	180 185 190	
15	Leu Ile Asn Tyr Ile Ile Val Phe Leu Val Cys Trp Val Phe Ala Val	
	195 200 205	
	Val Asn Arg Ile Val Asn Gly Leu Asn Trp Pro Pro Ala Leu Asn Ile	
	210 215 220	
20	Leu His Thr Tyr Leu Ser Val Ser His Gly Phe Trp Ala Ser Val Thr	
	225 230 235 240	
	Phe Ile Tyr Asn Asn Pro Leu Met Trp Arg Tyr Phe Gly Ala Lys Ile	
	245 250 255	
	Leu Thr Val Phe Thr Phe Gly Tyr Phe Thr Asp Val Gln Lys Lys	
	260 265 270	
25	Leu Glu Lys Asn Leu Ser Pro Tyr Ser Ser Ser Arg Gly Thr Ser Gly	
	275 280 285	
	Lys Thr Met Leu Gly His Pro Thr Gly Asp Asp Val Gln Cys Ser Ser	
	290 295 300	
30	Asp Leu Gln Cys Ser Leu Glu Arg His Pro Asn Met Val	
	305 310 315	
<b>(2) INFORMATION FOR SEQ ID NO:7:</b>		
(i) SEQUENCE CHARACTERISTICS:		
(A) LENGTH: 349 amino acids		
(B) TYPE: amino acid		
35	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: peptide		
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:		
40	Val Tyr Ile Thr Val Glu Leu Ala Ile Ala Val Leu Ala Thr Leu Gly	
	1 5 10 15	
	Asn Val Leu Val Cys Trp Ala Val Trp Leu Asn Ser Asn Leu Asn Val	
	20 25 30	
	Thr Asn Tyr Phe Val Val Ser Leu Ala Ala Ala Asp Ile Ala Val Gly	
	35 40 45	
45	Val Ile Ala Ile Pro Phe Ala Ile Thr Ile Ser Thr Gly Phe Cys Ala	
	50 55 60	
	Ala Cys His Asn Cys Leu Phe Phe Ala Cys Phe Val Leu Val Leu Thr	

- 58 -

	65	70	75	80
	Gln Ser Ser Ile Phe Ser Leu Leu Ala Ile Ala Ile Asp Arg Tyr Ile			
	85		90	95
5	Ala Ile Arg Ile Pro Leu Arg Tyr Asn Gly Leu Val Thr Gly Thr Arg			
	100		105	110
	Ala Lys Gly Ile Ile Ala Val Cys Trp Val Leu Ser Phe Ala Ile Gly			
	115		120	125
	Leu Thr Pro Met Leu Gly Trp Asn Asn Cys Ser Gln Pro Lys Glu Gly			
	130		135	140
10	Arg Asn Tyr Ser Gln Gly Cys Gly Glu Gly Gln Val Ala Cys Leu Phe			
	145		150	155
	Glu Asp Val Val Pro Met Asn Tyr Met Val Tyr Tyr Asn Phe Phe Ala			
	165		170	175
15	Phe Val Leu Val Pro Leu Leu Val Tyr Leu Arg Ile Phe Leu Ala			
	180		185	190
	Ala Arg Arg Gln Leu Lys Gln Met Glu Ser Gln Pro Leu Pro Gly Glu			
	195		200	205
	Arg Ala Arg Ser Thr Leu Gln Lys Glu Val His Ala Ala Lys Ser Ala			
	210		215	220
20	Ile Ile Val Gly Leu Phe Ala Leu Cys Trp Leu Pro Leu His Ile Ile			
	225		230	235
	Asn Cys Phe Thr Phe Phe Cys Pro Glu Cys Ser His Ala Pro Leu Trp			
	245		250	255
25	Leu Met Tyr Leu Thr Ile Val Leu Ser His Thr Asn Ser Trp Asn Pro			
	260		265	270
	Phe Ile Tyr Ala Tyr Arg Ile Arg Glu Phe Arg Gln Thr Phe Arg Lys			
	275		280	285
	Ile Ile Arg Ser His Val Leu Arg Arg Glu Pro Phe Lys Ala Gly			
	290		295	300
30	Gly Thr Ser Ala Arg Ala Leu Ala Ala His Gly Ser Asp Gly Glu Gln			
	305		310	315
	Ile Ser Leu Arg Leu Asn Gly His Pro Pro Gly Val Trp Ala Asn Gly			
	325		330	335
35	Ser Ala Pro His Pro Glu Arg Arg Pro Asn Gly Tyr Thr			
	340		345	
	(2) INFORMATION FOR SEQ ID NO:8:			
	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 314 amino acids			
	(B) TYPE: amino acid			
40	(C) STRANDEDNESS: single			
	(D) TOPOLOGY: linear			
	(ii) MOLECULE TYPE: peptide			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:			
45	Ala Tyr Ile Gly Ile Glu Val Leu Ile Ala Leu Val Ser Val Pro Gly			
	1	5	10	15
	Trp Leu Val Ile Trp Ala Val Lys Val Asn Gln Ala Leu Arg Asp Ala			
	20		25	30

- 59 -

Thr Phe Cys Phe Ile Val Ser Ile Ala Val Ala Asp Val Ala Val Gly  
 35 40 45  
 Ala Leu Val Ile Pro Leu Ala Ile Leu Ile Asn Ile Gly Pro Arg Thr  
 50 55 60 65 70 75 80  
 Tyr Phe His Thr Cys Leu Met Val Ala Cys Pro Val Leu Ile Leu Thr  
 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160  
 Gln Ser Ser Ile Ile Ala Leu Leu Ala Ile Ala Val Asp Arg Tyr Leu  
 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Ala Ala Val Ala Ile Ala Gly Cys Trp Ile Leu Ser Phe Val Val Gly  
 115 120 125 130 135 140 145 150 155 160  
 Leu Thr Pro Leu Phe Gly Trp Asn Arg Leu Gly Glu Ala Gln Arg Ala  
 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Arg Val Lys Ile Pro Leu Arg Tyr Lys Thr Val Val Thr Pro Arg Arg  
 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Ala Ala Val Ala Ile Ala Gly Cys Trp Ile Leu Ser Phe Val Val Gly  
 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Leu Thr Pro Leu Phe Gly Trp Asn Arg Leu Gly Glu Ala Gln Arg Ala  
 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Trp Ala Ala Asn Gly Ser Gly Gly Glu Pro Val Ile Lys Cys Glu Phe  
 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Glu Lys Val Ile Ser Met Glu Tyr Met Val Tyr Phe Asn Phe Phe Val  
 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Trp Val Leu Pro Pro Leu Leu Leu Met Val Leu Ile Tyr Leu Glu Val  
 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Phe Tyr Leu Ile Arg Arg Gln Leu Gly Lys Lys Val Ser Ala Ser Ser  
 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Gly Asp Pro Gln Lys Tyr Tyr Gly Lys Glu Leu Lys Ile Ala Lys Ser  
 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Leu Ala Leu Ile Leu Phe Leu Phe Ala Leu Ser Trp Leu Pro Leu His  
 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Ile Ile Asn Cys Ile Thr Leu Phe Cys Pro Ser Cys Arg Lys Pro Ser  
 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Ile Leu Met Tyr Ile Ala Ile Phe Leu Thr His Gly Asn Ser Ala Met  
 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310  
 Pro Ile Val Tyr Ala Phe Arg Ile Gln Lys Phe Arg Val Thr Phe Leu  
 275 280 285 290 295 300 305 310  
 Lys Ile Trp Asn Asp His Phe Arg Cys Gln Pro Thr Pro Pro Val Asp  
 290 295 300 305 310  
 Glu Asp Pro Pro Glu Glu Ala Pro His Asp  
 305 310  
 (2) INFORMATION FOR SEQ ID NO:9:  
 (i) SEQUENCE CHARACTERISTICS:  
     (A) LENGTH: 342 amino acids  
     (B) TYPE: amino acid  
     (C) STRANDEDNESS: single  
     (D) TOPOLOGY: linear  
 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:  
 Val Ala Phe Ile Gly Ile Thr Thr Gly Leu Leu Ser Ile Ala Thr Val  
 1 5 10 15  
 Thr Gly Asn Leu Leu Val Leu Ile Ser Phe Lys Val Asn Thr Glu Leu

- 60 -

	20	25	30
	Lys Thr Val Asn Asn Tyr Phe Leu Leu Ser Ile Ala Cys Ala Asp Leu		
	35	40	45
5	Ile Ile Gly Thr Phe Ser Met Leu Tyr Leu Leu Met His Trp Ala Leu		
	50	55	60
	Gly Thr Leu Ala Cys Asp Leu Trp Leu Ala Leu Asp Tyr Val Ala Ser		
	65	70	75
	Asn Ala Ser Val Leu Asn Leu Leu Ile Ser Phe Asp Arg Tyr Phe		
	85	90	95
10	Ser Val Thr Arg Pro Leu Ser Tyr Arg Ala Lys Arg Thr Pro Arg Arg		
	100	105	110
	Ala Ala Ile Met Ile Gly Ile Ala Trp Leu Val Ser Phe Val Leu Trp		
	115	120	125
15	Ala Pro Ala Ile Leu Phe Trp Gln Tyr Leu Val Gly Glu Arg Thr Met		
	130	135	140
	Leu Ala Gly Gln Cys Tyr Ile Gln Phe Leu Ser Gln Pro Ile Ile Thr		
	145	150	155
	Phe Gly Thr Ala Met Ala Ala Phe Tyr Met Pro Val Thr Val Met Thr		
	165	170	175
20	Leu Tyr Trp Arg Ile Tyr Arg Phe Thr Glu Asn Arg Ala Arg Glu Leu		
	180	185	190
	Gln Gly Ser Glu Thr Pro Gly Lys Gly Gly Ser Ser Ser Ser Ser		
	195	200	205
25	Glu Arg Ser Gln Pro Gly Ala Glu Gly Ser Pro Glu Thr Pro Lys Gly		
	210	215	220
	Gln Lys Pro Arg Gly Lys Glu Leu Ala Lys Arg Lys Thr Phe Ser Leu		
	225	230	235
	Val Lys Glu Lys Lys Ala Ala Arg Thr Leu Ser Ala Ile Leu Leu Ala		
	245	250	255
30	Phe Ile Leu Thr Trp Thr Pro Tyr Asn Ile Met Val Leu Val Ser Thr		
	260	265	270
	Phe Cys Lys Asp Cys Val Pro Glu Thr Leu Trp Glu Leu Gly Tyr Trp		
	275	280	285
35	Leu Ile Cys Tyr Val Asn Ser Thr Ile Asn Pro Trp Tyr Ala Leu Cys		
	290	295	300
	Asn Lys Ala Phe Arg Asp Thr Phe Arg Leu Leu Leu Cys Trp Asp		
	305	310	315
	Lys Arg Arg Trp Arg Lys Ile Pro Lys Arg Pro Gly Ser Val His Arg		
	325	330	335
40	Thr Pro Ser Arg Gln Cys		
	340		

## (2) INFORMATION FOR SEQ ID NO:10:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 317 amino acids

45 (B) TYPE: amino acid

(C) STRANDEDNESS: single

- 67 -

(D) TOPOLOGY: linear  
(ii) MOLECULE TYPE: peptid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Ile Gly Asn Ile Leu Val Met Val Ser Ile Lys Val Asn Arg His Tyr  
20 25 30

Phe Leu Phe Ser Ile Ala Cys Ala Asp Leu Ile Ile Gly Val Phe Ser  
35 40 45

10 Met Asn Leu Tyr Thr Leu Tyr Thr Val Ile Gly Tyr Trp Pro Leu Gly  
50 55 60

Pro Val Val Cys Asp Leu Tyr Val Val Ser Asn Ala Ser Val Val Met Asn  
65 70 75 80

15 Leu Leu Ile Ile Ser Phe Asp Arg Tyr Phe Cys Val Thr Lys Pro Leu  
85 90 95

Thr Tyr Pro Val Lys Arg Thr Thr Lys Met Ala Gly Met Met Ile Ala  
100 105 110

Ala Ala Trp Val Leu Ser Phe Ile Leu Trp Ala Pro Ala Ile Leu Phe  
 115 120 125

20 Trp Gln Phe Ile Val Gly Val Arg Thr Val Glu Asp Gly Glu Cys Tyr

Ile Gln Phe Phe Ser Asn Pro Ala Val Thr Phe Gly Thr Ala Ile Ala

Ser Arg Ala Ser Lys Ser Arg Ile Lys Lys Asp Lys Lys Glu Pro Val  
180 185 190

Ala Asn Gln Asp Pro Val Ser Pro Ser Leu Val Gln Gly Arg Ile Val  
195 200 205

Lys Pro Leu Ser Ser Asp Asp Lys Ile Val Arg Arg Thr Lys Gln Pro  
210 215 220

Ala Lys Lys Lys Pro Pro Pro Ser Arg Glu Lys Lys Val Thr Arg Thr  
225 230 235 240

Ile Ala Ile Leu Leu Ala Phe Ile Ile Thr Trp Ala Pro Tyr Asn Val  
245 250 255

Met Val Leu Ile Asn Thr Phe Cys Ala Pro Cys Ile Pro Asn Thr Val  
260 265 270

Trp Arg Ile Gly Tyr Trp Leu Cys Tyr Ile Asn Ser Thr Ile Asn Pro  
275 280 285

40 Ala Cys Tyr Ala Leu Cys Asn Ala Thr Phe Lys Lys Thr Phe Lys His  
           290           295                           300

Leu Ile Met Cys His Tyr Lys Asn Ile Gly Ala Thr Arg  
305 310 315

(2) INFORMATION FOR SEQ ID NO:11:

45 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 355 amino acids

- 62 -

(B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear  
 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Trp	Phe	Ile	Ala	Phe	Leu	Thr	Gly	Ile	Leu	Ala	Leu	Val	Thr	Ile	Ile
1				5					10				15		
Gly	Asn	Ile	Leu	Val	Ile	Val	Ser	Phe	Lys	Val	Asn	Lys	Gln	Leu	Lys
				20				25				30			
Thr	Val	Asn	Asn	Tyr	Phe	Leu	Leu	Ser	Leu	Ala	Cys	Ala	Asp	Leu	Ile
				35				40				45			
Ile	Gly	Val	Ile	Ser	Met	Asn	Leu	Phe	Thr	Thr	Tyr	Ile	Ile	Met	Asn
					50		55				60				
Arg	Trp	Ala	Leu	Gly	Asn	Thr	Ala	Cys	Asp	Leu	Trp	Ile	Ala	Ile	Asp
				65		70			75				80		
Tyr	Val	Ala	Ser	Asn	Ala	Ser	Val	Leu	Asn	Leu	Leu	Val	Ile	Ser	Phe
					85				90				95		
Asp	Arg	Tyr	Phe	Ser	Ile	Thr	Arg	Pro	Leu	Thr	Tyr	Arg	Ala	Lys	Arg
					100			105				110			
Thr	Thr	Lys	Arg	Ala	Gly	Val	Met	Ile	Gly	Leu	Ala	Trp	Val	Ile	Ser
					115			120				125			
Phe	Val	Leu	Trp	Ala	Pro	Ala	Ile	Leu	Phe	Trp	Gln	Tyr	Phe	Val	Gly
					130		135				140				
Lys	Arg	Thr	Val	Pro	Pro	Gly	Glu	Cys	Phe	Ile	Gln	Phe	Leu	Ser	Glu
					145		150				155				160
Pro	Thr	Ile	Thr	Phe	Gly	Thr	Ala	Ile	Ala	Ala	Phe	Tyr	Met	Pro	Val
					165				170				175		
Thr	Ile	Met	Arg	Ile	Leu	Tyr	Trp	Arg	Ile	Tyr	Lys	Glu	Thr	Glu	Lys
					180			185				190			
Arg	Thr	Lys	Glu	Leu	Ala	Gly	Leu	Gln	Ala	Ser	Gly	Thr	Glu	Ala	Glu
					195			200				205			
Thr	Glu	Asn	Phe	Val	His	Pro	Thr	Gly	Ser	Ser	Arg	Ser	Cys	Ser	Ser
					210		215				220				
Tyr	Glu	Leu	Gln	Gln	Gln	Lys	Arg	Phe	Ala	Leu	Lys	Thr	Arg	Ser	Gln
					225		230				235				240
Ile	Thr	Lys	Arg	Lys	Leu	Leu	Val	Lys	Glu	Lys	Lys	Ala	Ala	Gln	Thr
					245				250				255		
Leu	Ser	Ala	Ile	Leu	Leu	Ala	Phe	Ile	Ile	Thr	Trp	Thr	Pro	Tyr	Asn
					260			265				270			
Ile	Met	Val	Leu	Val	Asn	Thr	Phe	Cys	Asp	Ser	Cys	Ile	Pro	Lys	Thr
					275			280				285			
Tyr	Trp	Asn	Leu	Gly	Gly	Tyr	Trp	Leu	Cys	Tyr	Ile	Asn	Ser	Thr	Val
					290			295				300			
Asn	Pro	Val	Cys	Tyr	Ala	L	u	Cys	Asn	Lys	Thr	Phe	Arg	Thr	Phe
					305			310				315			320
Lys	Thr	Leu	Leu	Leu	Cys	Gln	Cys	Asp	Lys	Arg	Lys	Arg	Arg	Lys	Gln

- 63 -

325	330	335
Gln Tyr Gln Gln Arg Gln Ser Val Ile Phe His Lys Arg Val Pro Glu		
340	345	350

5           Gln Ala Leu  
              355

(2) INFORMATION FOR SEQ ID NO:12:  
 (i) SEQUENCE CHARACTERISTICS:  
     (A) LENGTH: 333 amino acids  
     (B) TYPE: amino acid  
 10        (C) STRANDEDNESS: single  
     (D) TOPOLOGY: linear  
 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:  
 15        Met Val Phe Ile Ala Thr Val Arg Gly Ser Leu Ser Leu Val Thr Val  
         1               5               10               15  
 Val Gly Asn Ile Leu Val Met Leu Ser Ile Lys Val Asn Arg Gln Leu  
         20               25               30  
 Gln Thr Val Asn Asn Tyr Phe Leu Phe Ser Ile Ala Cys Ala Asp Leu  
         35               40               45  
 20        Ile Ile Gly Ala Phe Ser Met Asn Leu Tyr Thr Val Tyr Ile Ile Lys  
         50               55               60  
 Gly Tyr Trp Pro Leu Gly Ala Trp Cys Asp Leu Trp Leu Ala Leu Asp  
         65               70               75               80  
 Tyr Val Val Ser Asn Ala Ser Val Met Leu Leu Ile Ile Ser Phe Asp  
 25        85               90               95  
 Arg Tyr Phe Cys Val Thr Lys Pro Leu Thr Tyr Pro Ala Arg Arg Thr  
         100               105               110  
 Thr Lys Met Ala Gly Ile Met Ile Ala Ala Ala Trp Val Leu Ser Phe  
         115               120               125  
 30        Val Leu Trp Ala Pro Ala Ile Leu Phe Trp Gln Phe Val Val Gly Lys  
         130               135               140  
 Arg Thr Val Pro Asp Asn Gln Cys Phe Ile Gln Phe Leu Ser Asn Pro  
         145               150               155               160  
 35        Ala Val Thr Phe Gly Thr Ala Ile Ala Ala Phe Tyr Leu Pro Val Val  
         165               170               175  
 Ile Met Ile Val Leu Tyr Ile His Ile Ser Leu Ala Ser Arg Ser Arg  
         180               185               190  
 Val His Lys His Arg Pro Glu Gly Pro Lys Glu Lys Lys Ala Lys Thr  
         195               200               205  
 40        Ile Ala Phe Leu Lys Ser Pro Ile Met Gln Ser Val Lys Lys Pro Pro  
         210               215               220  
 Pro Gly Glu Ala Lys Phe Ala Ser Ile Ala Arg Asn Gln Val Arg Lys  
         225               230               235               240  
 Lys Arg Gln Leu Ala Ala Arg Glu Arg Lys Val Thr Arg Thr Ile Phe  
 45        245               250               255  
 Ala Ile Leu Leu Ala Phe Ile Leu Thr Trp Thr Pro Tyr Asn Val Met  
         260               265               270

64 -

Val Leu Val Asn Thr Phe Cys Gln Ser Cys Ile Pro Asp Thr Val Trp  
275 280 285

Ser Ile Gly Tyr Trp Leu Ile Cys Tyr Val Asn Ser Thr Ile Asn Pro  
290 295 300

5 Ala Cys Tyr Ala Leu Cys Asn Ala Thr Phe Lys Lys Thr Phe Arg His  
305 310 315 320

Leu Leu Leu Cys Gln Arg Tyr Asn Ile Gly Thr Ala Arg  
325 330

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS

- (A) LENGTH: 348 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Val Ile Thr Ile Ala Val Val Thr Ala Val Val Ser Leu Met Thr Ile  
1 5 10 15

20 Val Gly Asn Val Leu Val Met Ile Ser Phe Lys Val Asn Ser Gln Leu  
20 25 30

Lys Thr Val Asn Asn Tyr Tyr Leu Leu Ser Ile Ala Cys Ala Asp Leu  
 35 40 45

Ile Ile Gly Ile Phe Ser Met Asn Leu Tyr Thr Thr Tyr Ile Leu Ile  
50 55 60

25 Met Gly Arg Trp Ala Leu Gly Ser Leu Ala Cys Asp Leu Trp Leu Ala  
65 70 75 80

Ile Asp Tyr Val Ala Ser Asn Ala Ser Val Leu Asn Leu Leu Val Ile  
85 90 95

30 Ser Phe Asp Arg Tyr Phe Ser Ile Thr Arg Pro Leu Thr Tyr Arg Ala  
100 105 110

Lys Arg Thr Pro Lys Arg Ala Gly Ile Met Ile Gly Ile Ala Trp Leu  
115 120 125

Ile Ser Phe Ile Leu Trp Ala Pro Ala Ile Leu Cys Trp Gln Tyr Leu  
130 135 140

Val Gly Lys Arg Thr Val Pro Ile Asp Glu Cys Gln Ile Gln Phe Leu  
145 150 155 160

Ser Glu Pro Thr Ile Thr Phe Gly Thr Ala Ile Ala Ala Phe Tyr Ile  
165 170 175

Pro Val Ser Ile Met Arg Ile Leu Tyr Cys Arg Ile Tyr Arg Glu Thr  
180 185 190

Glu Lys Arg Thr Lys Asp Leu Ala Asp Leu Gln Gly Ser Asp Ser Val  
195 200 205

Tyr Lys Ala Glu Lys Arg Lys Pro Ala His Arg Ala Leu Phe Arg Ser  
210 215 220

45 Cys Leu Arg Cys Pro Arg Pro Thr Lys Gly Leu Asn Pro Asn Pro Ser  
225 230 235 240

His Gln Met Thr Lys Arg Lys Arg Met Ser Leu Val Lys Glu Arg Lys

- 65 -

	245	250	255	
	Ala Ala Gln Thr Leu Ser Ala Ile Leu Leu Ala Phe Ile Ile Thr Trp			
	260	265	27'	
5	Thr Pro Tyr Asn Ile Met Val Leu Val Ser Thr Phe Cys Asp Lys Cys			
	275	280	285	
	Val Pro Val Thr Leu Trp His Leu Gly Tyr Trp Leu Cys Tyr Ile Asn			
	290	295	300	
	Ser Thr Val Asn Pro Ile Cys Tyr Ala Leu Cys Asn Arg Thr Phe Arg			
	305	310	315	320
10	Lys Thr Phe Ile Met Leu Leu Cys Arg Trp Lys Lys Lys Lys Val Glu			
	325	330	335	
	Glu Lys Leu Tyr Trp Gln Gly Asn Ser Lys Leu Pro			
	340	345		
	<b>(2) INFORMATION FOR SEQ ID NO:14:</b>			
15	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 377 amino acids			
	(B) TYPE: amino acid			
	(C) STRANDEDNESS: single			
	(D) TOPOLOGY: linear			
20	(ii) MOLECULE TYPE: peptide			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:			
	Thr Ala Gly Asp Cys Leu Ile Met Leu Ile Val Leu Leu Ile Val Ala			
	1	5	10	15
25	Gly Asn Val Leu Val Ile Val Ala Ile Ala Lys Thr Pro Arg Leu Gln			
	20	25	30	
	Thr Leu Thr Asn Leu Phe Ile Met Ser Ile Ala Ser Ala Asp Leu Val			
	35	40	45	
	Met Leu Leu Leu Val Val Pro Phe Cys Ala Thr Leu Val Val Trp Gly			
	50	55	60	
30	Arg Trp Glu Tyr Gly Ser Phe Phe Cys Glu Leu Trp Thr Ser Val Asp			
	65	70	75	80
	Val Leu Cys Val Thr Ala Ser Ile Glu Thr Leu Cys Val Ile Ala Leu			
	85	90	95	
35	Asp Arg Tyr Leu Ala Ile Thr Ser Pro Phe Arg Tyr Gln Ser Leu Leu			
	100	105	110	
	Thr Arg Ala Arg Ala Arg Gly Leu Val Cys Thr Val Trp Ala Ile Ser			
	115	120	125	
	Ala Leu Val Ser Phe Leu Pro Ile Leu Leu Ser Asp Glu Ala Arg Arg			
	130	135	140	
40	Cys Tyr Asn Asp Pro Lys Cys Cys Asp Phe Val Thr Asn Arg Ala Tyr			
	145	150	155	160
	Ala Ile Ala Ser Ser Val Val Ser Phe Tyr Val Pro Leu Cys Ile Met			
	165	170	175	
45	Phe Val Tyr Leu Arg Val Phe Arg Glu Ala Gln Lys Gln Val Lys Lys			
	180	185	190	
	Ile Asp Ser Cys Glu Arg Arg Phe Leu Gly Gly Pro Ala Arg Pro Pro			
	195	200	205	

- 66 -

	Ser Pro Ser Pro Ser Pro Val Pro Ala Pro Ala Pro Pro Gly Pro Pro
	210 215 220
	Arg Pro Ala Ala Ala Ala Ala Thr Ala Pro Leu Ala Asn Glv Arg Ala
	225 230 235 240
5	Gly Lys Arg Arg Pro Ser Arg Leu Val Ala Leu Arg Glu Gln Lys Ala
	245 250 255
	Leu Lys Thr Leu Gly Ile Ile Met Gly Val Phe Thr Leu Cys Trp Leu
	260 265 270
10	Pro Phe Phe His Arg Glu Leu Val Pro Asp Arg Leu Phe Val Phe Phe
	275 280 285
	Asn Trp Leu Arg Tyr Ala Asn Ser Ala Phe Asn Pro Ile Ile Tyr Cys
	290 295 300
	Arg Ser Pro Asp Phe Arg Lys Ala Phe Gln Gly Leu Leu Cys Cys Ala
	305 310 315 320
15	Arg Arg Ala Ala Arg Arg His Ala Thr His Gly Asp Arg Pro Arg
	325 330 335
	Ala Ser Gly Cys Ile Ala Arg Pro Gly Pro Pro Ser Pro Gly Ala Ala
	340 345 350
20	Ser Asp Asp Asp Asp Asp Val Val Gly Ala Thr Pro Pro Ala Arg
	355 360 365
	Leu Leu Glu Pro Trp Ala Gly Cys Asn
	370 375
(2) INFORMATION FOR SEQ ID NO:15:	
(i) SEQUENCE CHARACTERISTICS:	
25	(A) LENGTH: 362 amino acids
	(B) TYPE: amino acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear
	(ii) MOLECULE TYPE: peptide
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:
	Val Val Gly Ile Val Met Ser Leu Ile Val Leu Ala Ile Val Phe Gly
	1 5 10 15
	Asn Val Leu Val Ile Thr Ala Ile Ala Lys Phe Glu Arg Leu Gln Thr
	20 25 30
35	Val Thr Asn Tyr Phe Ile Thr Ser Ile Ala Cys Ala Asp Leu Val Met
	35 40 45
	Gly Leu Ala Val Val Pro Phe Gly Ala Ala His Ile Leu Met Lys Met
	50 55 60
40	Trp Thr Phe Gly Asn Phe Trp Cys Glu Phe Trp Thr Ser Ile Asp Val
	65 70 75 80
	Leu Cys Val Thr Ala Ser Ile Glu Thr Leu Cys Val Ile Ala Val Asp
	85 90 95
	Arg Tyr Phe Ala Ile Thr Ser Pro Phe Lys Tyr Gln Ser Leu Leu Thr
	100 105 110
45	Lys Asn Lys Ala Arg Val Ile Ile Met Val Trp Ile Val Ser Gly
	115 120 125
	Leu Thr Ser Phe Leu Pro Ile Leu Tyr Arg Ala Thr His Gln Glu Ala

- 57 -

	130	135	140
	Ile Asn Cys Tyr Ala Asn Glu Thr Cys Cys Asp Phe Phe Thr Asn Gln		
145	150	155	160
5	Ala Tyr Ala Ala Ser Ser Ala Val Ser Phe Tyr Val Pro Leu Val Ile		
	165	170	175
	Met Val Phe Val Tyr Ser Arg Val Phe Gln Glu Ala Lys Arg Gln Leu		
	180	185	190
	Gln Lys Ile Asp Lys Ser Glu Gly Arg Phe Ile Phe Val Gln Asn Leu		
	195	200	205
10	Ser Gln Val Glu Gln Asp Gly Arg Thr Gly His Gly Leu Arg Arg Ser		
	210	215	220
	Ser Lys Phe Cys Leu Lys Glu His Lys Ala Leu Lys Thr Leu Gly Ile		
	225	230	235
	Ile Pro Cys Thr Phe Thr Leu Cys Trp Leu Pro Phe Phe Ile Val Asn		
15	245	250	255
	Ile Val Val Ile Gln Asp Asn Leu Ile Arg Lys Glu Val Tyr Ile Leu		
	260	265	270
	Leu Asn Trp Ile Gly Tyr Val Asn Ser Gly Phe Asn Pro Leu Ile Tyr		
	275	280	285
20	Cys Arg Ser Pro Asp Phe Arg Ile Ala Phe Gln Glu Leu Leu Cys Leu		
	290	295	300
	Arg Arg Ser Ser Leu Lys Ala Tyr Gly Asn Gly Tyr Ser Ser Asn Gly		
	305	310	315
	Asn Thr Gly Glu Gln Ser Gly Tyr His Val Glu Gln Glu Lys Glu Asn		
25	325	330	335
	Lys Leu Leu Cys Glu Asp Leu Pro Gly Thr Glu Asp Phe Val Gly His		
	340	345	350
	Gln Gly Thr Val Pro Ser Asp Asn Ile Asp		
	355	360	
30	(2) INFORMATION FOR SEQ ID NO:16:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 362 amino acids		
	(B) TYPE: amino acid		
	(C) STRANDEDNESS: single		
35	(D) TOPOLOGY: linear		
	(ii) MOLECULE TYPE: peptide		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:		
	Ala Ala Leu Ala Gly Ala Leu Leu Ala Leu Ala Val Leu Ala Thr Val		
	1	5	10
	15		
40	Gly Gly Asn Leu Leu Val Ile Val Ala Ile Ala Trp Thr Pro Arg Leu		
	20	25	30
	Gln Thr Met Thr Asn Val Phe Val Thr Ser Leu Ala Ala Asp Leu		
	35	40	45
45	Asp Leu Leu Val Val Pro Pro Ala Ala Thr Leu Ala Leu Thr Gly His		
	50	55	60
	Trp Pro Leu Gly Ala Thr Gly Cys Glu Leu Trp Thr Ser Val Asp Val		
	65	70	75
	80		

- 68 -

	Leu Cys Val Thr Ala Ser Ile Glu Thr Leu Cys Ala Ile Ala Val Asp	
	85	90
	95	
	Arg Tyr Leu Ala Val Thr Asn Pro Leu Arg Tyr Gly Ala Leu Val Thr	
	100	105
	110	
5	Lys Arg Cys Ala Arg Thr Ala Trp Leu Val Trp Val Val Ser Ala Ala	
	115	120
	125	
	Val Ser Phe Ala Pro Ile Met Ser Gln Trp Trp Arg Val Gly Ala Asp	
	130	135
	140	
10	Ala Glu Ala Gln Arg Cys His Ser Asn Pro Arg Cys Cys Ala Phe Ala	
	145	150
	155	160
	Ser Asn Met Pro Tyr Ala Val Leu Leu Ser Ser Ser Val Ser Phe Tyr	
	165	170
	175	
	Leu Pro Leu Leu Leu Phe Val Tyr Ala Arg Val Phe Trp Ala Thr Arg	
	180	185
	190	
15	Gln Leu Arg Leu Leu Arg Gly Glu Leu Gly Arg Phe Pro Pro Glu Glu	
	195	200
	205	
	Ser Pro Pro Ala Pro Ser Arg Ser Leu Ala Pro Ala Pro Val Gly Thr	
	210	215
	220	
20	Gly Ala Pro Pro Glu Gly Val Pro Ala Cys Gly Arg Pro Pro Ala Arg	
	225	230
	235	240
	Leu Ile Pro Ile Arg Glu His Arg Ala Leu Cys Thr Leu Gly Leu Ile	
	245	250
	255	
	Met Gly Thr Phe Thr Leu Cys Trp Leu Pro Phe Phe Ile Ala Asn Val	
	260	265
	270	
25	Leu Arg Ala Leu Gly Gly Pro Ser Leu Val Pro Gly Pro Ala Phe Leu	
	275	280
	285	
	Ala Leu Asn Trp Leu Ile Gly Tyr Ala Asn Ser Ala Phe Asn Pro Leu	
	290	295
	300	
30	Ile Tyr Cys Arg Ser Pro Asp Phe Arg Ser Ala Phe Arg Arg Leu Leu	
	305	310
	315	320
	Cys Arg Cys Gly Arg Arg Leu Pro Pro Glu Pro Cys Ala Ala Arg	
	325	330
	335	
	Pro Ala Leu Phe Pro Ser Gly Val Pro Ala Ala Glu Ser Ser Pro Ala	
	340	345
	350	
35	Gln Pro Arg Leu Cys Gln Arg Leu Asp Gly	
	355	360
	(2) INFORMATION FOR SEQ ID NO:17:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 375 amino acids	
40	(B) TYPE: amino acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: peptide	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:	
45	Ala Ile Leu Leu Gly Val Ile Leu Gly Gly Leu Ile Leu Phe Gly Val	
	1	5
	10	15
	Leu Gly Asn Ile Leu Val Ile Leu Ser Val Ala Cys His Arg His Leu	

- 69 -

	20	25	30
	His Ser Val Thr His Tyr Tyr Ile Val Asn Leu Ala Val Ala Asp Leu		
	35	40	45
5	Leu Leu Thr Ser Thr Val Leu Pro Phe Ser Ala Ile Phe Glu Ile Leu		
	50	55	60
	Gly Tyr Trp Lys Phe Gly Arg Val Phe Cys Asn Val Trp Ala Ala Val		
	65	70	75
	Asp Val Leu Cys Cys Thr Ala Ser Ile Met Leu Leu Cys Ile Ile Ser		
	85	90	95
10	Ile Asp Arg Tyr Ile Gly Val Ser Tyr Pro Leu Arg Tyr Pro Thr Ile		
	100	105	110
	Val Thr Gln Lys Arg Gly Leu Met Ala Leu Leu Cys Val Trp Ala Leu		
	115	120	125
15	Ser Leu Val Ile Ser Ile Gly Pro Leu Phe Gly Trp Arg Gln Pro Ala		
	130	135	140
	Pro Glu Asp Glu Thr Ile Cys Gln Ile Asn Glu Glu Pro Gly Tyr Val		
	145	150	155
	Leu Phe Ser Ala Leu Gly Ser Phe Tyr Val Pro Leu Thr Ile Ile Leu		
	165	170	175
20	Val Met Tyr Cys Arg Val Tyr Val Val Ala Lys Arg Glu Ser Arg Gly		
	180	185	19'
	Leu Lys Ser Gly Leu Lys Thr Asp Lys Ser Asp Ser Glu Gln Val Thr		
	195	200	205
25	Leu Arg Ile His Arg Lys Asn Ala Gln Val Gly Gly Ser Gly Val Thr		
	210	215	220
	Ser Ala Lys Asn Lys Thr His Phe Ser Val Arg Leu Leu Lys Phe Ser		
	225	230	235
	Arg Glu Lys Lys Ala Ala Lys Thr Leu Gly Ile Val Val Gly Cys Phe		
	245	250	255
30	Val Leu Cys Trp Leu Pro Phe Phe Leu Val Met Pro Ile Gly Ser Phe		
	260	265	270
	Phe Pro Asp Phe Arg Pro Ser Glu Thr Val Phe Lys Ile Ala Phe Trp		
	275	280	285
35	Leu Gly Tyr Ile Asn Ser Cys Ile Asn Pro Ile Ile Tyr Pro Cys Ser		
	290	295	300
	Ser Gln Glu Phe Lys Lys Ala Phe Gln Asn Val Leu Arg Ile Gln Cys		
	305	310	315
	Leu Arg Arg Lys Gln Ser Ser Lys His Thr Leu Gly Tyr Thr Leu His		
	325	330	335
40	Ala Pro Ser His Val Leu Glu Gly Gln His Lys Asp Leu Val Arg Ile		
	340	345	350
	Pro Val Gly Ser Ala Glu Thr Phe Tyr Lys Ile Ser Lys Thr Asp Gly		
	355	360	365
45	Val Cys Glu Trp Lys Ile Phe		
	370	375	

- 70 -

## (2) INFORMATION FOR SEQ ID NO:18:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 370 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

	Ala Ile Ser Val Gly Leu Val Leu Gly Ala Phe Ile Leu Phe Ala Ile			
10	5	10	15	
	Val Gly Asn Ile Leu Val Ile Leu Ser Val Ala Cys Asn Arg His Leu			
	20	25	30	
	Arg Thr Pro Thr Asn Tyr Phe Ile Val Asn Ile Ala Ile Ala Asp Leu			
	35	40	45	
15	Leu Leu Ser Phe Thr Val Leu Pro Phe Ser Ala Thr Leu Glu Val Leu			
	50	55	60	
	Gly Tyr Trp Val Leu Gly Arg Ile Phe Cys Asp Ile Trp Ala Ala Val			
	65	70	75	80
20	Asp Val Leu Cys Cys Thr Ala Ser Ile Leu Ser Leu Cys Ala Ile Ser			
	85	90	95	
	Ile Asp Arg Tyr Ile Gly Val Arg Tyr Ser Leu Gln Tyr Pro Thr Leu			
	100	105	110	
	Val Thr Arg Arg Tyr Ala Ile Ile Ala Leu Leu Ser Val Trp Val Leu			
	115	120	125	
25	Ser Thr Val Ile Ser Ile Gly Pro Leu Leu Gly Trp Lys Glu Pro Ala			
	130	135	140	
	Pro Asn Asp Asp Lys Glu Cys Val Thr Glu Glu Pro Phe Leu Phe Cys			
	145	150	155	160
30	Ser Leu Gly Ser Phe Tyr Ile Pro Ile Ala Val Ile Leu Val Met Tyr			
	165	170	175	
	Cys Arg Val Tyr Ile Val Ala Lys Arg Thr Thr Lys Asn Leu Glu Ala			
	180	185	190	
	Gly Val Met Lys Glu Met Ser Asn Ser Lys Phe Leu Thr Leu Arg Ile			
	195	200	205	
35	His Trp Ser Lys Asn Phe His Glu Asp Thr Leu Ser Ser Thr Lys Ala			
	210	215	220	
	Lys Gly His Asn Pro Arg Ser Ser Ile Ala Val Lys Leu Phe Lys Phe			
	225	230	235	240
40	Ser Arg Glu Lys Lys Ala Ala Lys Thr Leu Gly Ile Val Val Gly Trp			
	245	250	255	
	Ile Leu Cys Trp Leu Pro Phe Phe Ile Ala Leu Pro Leu Gly Ser Leu			
	260	265	270	
	Phe Ser Thr Leu Lys Pro Pro Asp Ala Val Phe Lys Trp Phe Trp Leu			
	275	280	285	
45	Gly Tyr Phe Asn Ser Cys Leu Asn Pro Ile Ile Tyr Pro Cys Ser Ser			
	290	295	300	
	Lys Glu Phe Lys Arg Ala Leu Leu Gly Cys Gln Cys Arg Gly Gly Arg			

- 71 -

305	310	315	320
-----	-----	-----	-----

Arg Arg Arg Arg Arg Arg Arg Leu Ala Cys Ala Tyr Thr Tyr Arg Pro	325	330	335
---	-----	-----	-----

5 Trp Thr Arg Gly Gly Ser Leu Glu Arg Ser Gln Ser Arg Lys Asp Ser	340	345	350
---	-----	-----	-----

Ile Asp Asp Ser Gly Ser Cys Met Ser Gly Gln Lys Arg Thr Leu Pro	355	360	365
---	-----	-----	-----

Ser Ala 370
----------------

10 (2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 330 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Val Ala Gly Leu Ala Ala Val Val Gly Phe Leu Ile Val Phe Thr Val	1	5	10	15
20 Val Gly Asn Val Leu Val Val Ile Ala Val Leu Thr Ser Arg Ala Leu	20	25	30	
Arg Ala Pro Gln Asn Leu Phe Leu Val Ser Ile Ala Ser Ala Asp Ile	35	40	45	

25 Leu Val Ala Thr Leu Val Met Pro Phe Ser Leu Ala Asn Glu Ile Met	50	55	60	
--	----	----	----	--

Tyr Trp Tyr Phe Gly Gln Val Trp Cys Gly Val Tyr Leu Ala Ile Asp	65	70	75	80
---	----	----	----	----

Val Leu Phe Cys Thr Ser Ser Ile Val His Leu Cys Ala Ile Ser Leu	85	90	95	
---	----	----	----	--

30 Asp Arg Tyr Trp Ser Val Thr Gln Ala Val Glu Tyr Asn Leu Lys Arg	100	105	110	
--	-----	-----	-----	--

Thr Pro Arg Arg Val Lys Ala Thr Ile Val Ala Val Trp Leu Ile Ser	115	120	125	
---	-----	-----	-----	--

35 Ala Val Ile Ser Phe Pro Pro Leu Val Ser Leu Tyr Arg Gln Pro Asp	130	135	140	
--	-----	-----	-----	--

Gly Ala Ala Tyr Pro Gln Cys Gly Leu Asn Asp Glu Thr Trp Tyr Ile	145	150	155	160
---	-----	-----	-----	-----

Leu Ser Ser Cys Ile Gly Ser Phe Phe Ala Pro Cys Leu Ile Tyr Leu	165	170	175	
---	-----	-----	-----	--

40 Leu Val Tyr Ala Arg Ile Tyr Arg Val Ala Lys Arg Arg Thr Arg Thr	180	185	190	
--	-----	-----	-----	--

Leu Ser Glu Lys Arg Ala Pro Val Gly Pro Asp Gly Ala Ser Pro Thr	195	200	205	
---	-----	-----	-----	--

Thr Glu Asn Gly Leu Gly Ala Ala Gly Glu Ala Arg Thr Gly Thr	210	215	220	
---	-----	-----	-----	--

Ala Arg Phe Leu Ser Arg Arg Arg Ala Arg Ser Ser Val Cys Arg	225	230	235	240
---	-----	-----	-----	-----

Arg Lys Val Ala Gln Ala Arg Glu Lys Arg Phe Thr Phe Val Leu Ala				
---	--	--	--	--

- 72 -

245

250

255

Leu Val Phe Val Leu Cys Trp Phe Pro Phe Phe Ile Tyr Ser Leu  
 260 265 270

5 Tyr Gly Ile Cys Arg Glu Ala Cys Gln Val Pro Gly Pro Leu Phe Lys  
 275 280 285

Phe Phe Phe Trp Ile Gly Tyr Cys Asn Ser Ser Leu Asn Pro Val Ile  
 290 295 300

Tyr Thr Val Phe Asn Gln Asp Phe Arg Pro Ser Phe Lys His Ile Leu  
 305 310 315 320

10 Phe Arg Arg Arg Arg Gly Phe Arg Gln  
 325 330

## (2) INFORMATION FOR SEQ ID NO:20:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 330 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

20 Thr Ala Ala Ile Ala Ala Ala Ile Thr Phe Leu Ile Leu Phe Thr Ile  
 1 5 10 15

Phe Gly Asn Ala Leu Val Ile Ile Ala Val Leu Thr Ser Arg Ser Leu  
 20 25 30

25 Arg Ala Pro Gln Asn Leu Phe Leu Val Ser Ile Ala Ala Ala Asp Ile  
 35 40 45

Leu Val Ala Thr Leu Ile Ile Pro Phe Ser Leu Ala Asn Glu Leu Leu  
 50 55 60

Gly Tyr Trp Tyr Phe Arg Arg Thr Trp Cys Glu Val Tyr Leu Ala Leu  
 65 70 75 80

30 Asp Val Leu Phe Cys Thr Ser Ser Ile Val His Leu Cys Ala Ile Ser  
 85 90 95

Leu Asp Arg Tyr Trp Ala Val Ser Arg Ala Leu Glu Tyr Asn Ser Lys  
 100 105 110

35 Arg Thr Pro Arg Arg Ile Lys Cys Ile Ile Leu Thr Val Trp Leu Ile  
 115 120 125

Ala Ala Val Ile Ser Leu Pro Pro Leu Ile Tyr Lys Gly Asp Gln Gly  
 130 135 140

Pro Gln Pro Arg Gly Arg Pro Gln Cys Lys Leu Asn Gln Glu Ala Trp  
 145 150 155 160

40 Tyr Ile Leu Ser Ser Ile Gly Ser Phe Phe Ala Pro Cys Leu Ile Leu  
 165 170 175

Leu Val Tyr Leu Arg Ile Tyr Leu Ile Ala Lys Arg Ser Asn Arg Arg  
 180 185 190

45 Gly Pro Arg Ala Lys Cys Gly Pro Gly Gln Gly Glu Ser Lys Gln Pro  
 195 200 205

Arg Pro Asp His Gly Gly Ala Ile Ala Ser Ala Lys Leu Pro Ala Ile

- 73 -

	210	215	220	
	Ala Ser Gly Arg Gly Val Gly Ala Ile Gly Gly Gln Trp Trp Arg Arg			
225	230	235	240	
5	Arg Ala His Val Thr Arg Glu Lys Arg Phe Thr Phe Val Leu Ala Val			
	245	250	255	
	Val Ile Gly Val Phe Val Leu Cys Trp Phe Pro Phe Phe Ser Tyr			
	260	265	270	
	Ser Leu Gly Ala Ile Cys Pro Lys His Cys Lys Val Pro His Gly Leu			
10	275	280	285	
	Phe Gln Phe Phe Phe Trp Ile Gly Tyr Cys Asn Ser Ser Leu Asn Pro			
	290	295	300	
	Val Ile Tyr Thr Ile Phe Asn Gln Asp Phe Arg Met Phe Arg Arg Ile			
	305	310	315	320
15	Leu Cys Arg Pro Trp Thr Gln Thr Ala Trp			
	325	330		
	(2) INFORMATION FOR SEQ ID NO:21:			
	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 330 amino acids			
	(B) TYPE: amino acid			
20	(C) STRANDEDNESS: single			
	(D) TOPOLOGY: linear			
	(ii) MOLECULE TYPE: peptide			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:			
	Thr Leu Thr Leu Val Cys Ile Ala Cys Leu Ser Leu Thr Val Phe Gly			
25	1	5	10	15
	Asn Val Leu Val Ile Ile Ala Val Phe Thr Ser Arg Ala Leu Lys Ala			
	20	25	30	
	Pro Gln Asn Leu Phe Leu Val Ser Ile Ala Ser Ala Asp Ile Leu Val			
	35	40	45	
30	Ala Thr Leu Val Ile Pro Phe Ser Leu Ala Asn Glu Val Asn Gly Tyr			
	50	55	60	
	Trp Tyr Phe Gly Lys Trp Cys Glu Ile Tyr Leu Ala Leu Asp Val Leu			
	65	70	75	80
35	Phe Cys Thr Ser Ser Ile Val His Leu Cys Ala Ile Ser Leu Asp Arg			
	85	90	95	
	Tyr Trp Ser Ile Thr Gln Ala Ile Glu Tyr Asn Leu Lys Arg Thr Pro			
	100	105	110	
	Arg Arg Ile Lys Ala Ile Ile Ile Thr Val Trp Val Ile Ser Ala Val			
	115	120	125	
40	Ile Ser Phe Pro Pro Leu Ile Ser Ile Glu Lys Lys Gly Gly Gly			
	130	135	140	
	Gly Pro Gln Pro Ala Glu Pro Arg Cys Glu Ile Asn Asp Gln Lys Trp			
	145	150	155	160
45	Tyr Val Ile Ser Ser Cys Ile Gly Ser Phe Phe Ala Pro Cys Leu Ile			
	165	170	175	
	Trp Leu Val Tyr Val Arg Ile Tyr Gln Ile Ala Lys Arg Arg Thr Arg			
	180	185	190	

- 74 -

	Val Pro Pro Ser Arg Arg Asp Pro Asp Ala Val Ala Ala Pro Pro Gly			
	195	200	205	
	Gly Thr Glu Arg Arg Pro Asn Gly Leu Gly Pro Glu Arg Ser Ala Gly			
	210	215	220	
5	Pro Gly Gly Gly Arg Gly Arg Ser Ala Ser Gly Leu Pro Arg Arg Arg			
	225	230	235	240
	Ala Gly Ala Gly Gly Gln Asn Arg Glu Lys Arg Phe Thr Phe Val Ile			
	245	250	255	
10	Ala Val Val Ile Gly Val Phe Val Val Cys Trp Phe Pro Phe Phe			
	260	265	270	
	Thr Tyr Thr Leu Thr Ala Val Leu Cys Ser Val Pro Arg Thr Leu Phe			
	275	280	285	
	Lys Phe Phe Phe Trp Phe Gly Tyr Cys Asn Ser Ser Leu Asn Pro Val			
	290	295	300	
15	Ile Tyr Thr Ile Phe Asn His Asp Phe Arg Arg Ala Phe Lys Lys Ile			
	305	310	315	320
	Leu Cys Arg Gly Asp Arg Lys Arg Ile Val			
	325	330		
20	(2) INFORMATION FOR SEQ ID NO:22:			
	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 334 amino acids			
	(B) TYPE: amino acid			
	(C) STRANDEDNESS: single			
	(D) TOPOLOGY: linear			
25	(ii) MOLECULE TYPE: peptide			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:			
	Thr Leu Thr Leu Val Cys Ile Ala Gly Leu Ile Met Leu Phe Thr Val			
	1	5	10	15
30	Phe Gly Asn Val Leu Val Ile Ile Ala Val Phe Thr Ser Arg Ala Leu			
	20	25	30	
	Lys Ala Pro Gln Asn Leu Phe Leu Val Ser Ile Ala Ser Ala Asp Ile			
	35	40	45	
	Leu Val Ala Thr Leu Val Ile Pro Phe Ser Leu Ala Asn Glu Val Met			
	50	55	60	
35	Tyr Trp Tyr Phe Gly Lys Val Trp Cys Glu Ile Tyr Leu Ala Ile Asp			
	65	70	75	80
	Val Leu Phe Cys Thr Ser Ser Ile Val His Leu Cys Ala Ile Ser Leu			
	85	90	95	
40	Asp Arg Tyr Trp Ser Ile Thr Gln Ala Ile Glu Tyr Asn Leu Lys Arg			
	100	105	110	
	Thr Pro Arg Arg Ile Lys Ala Ile Ile Val Thr Val Trp Val Ile Ser			
	115	120	125	
	Ala Val Ile Ser Phe Pro Pro Leu Leu Ile Ser Ile Glu Lys Lys Gly			
	130	135	140	
45	Ala Gly Gly Gly Gln Gln Pro Ala Glu Pro Ser Cys Lys Ile Asn Asp			
	145	150	155	160
	Gln Lys Trp Tyr Val Ile Ser Ser Ile Gly Ser Phe Phe Ala Pro			

- 75 -

	165	170	175	
	Cys Leu Ile Asn His Leu Val Tyr Val Arg Ile Tyr Gln Ile Ala Lys			
	180	185	190	
5	Arg Arg Thr Arg Val Pro Pro Ser Arg Arg Gly Pro Asp Ala Cys Ser			
	195	200	205	
	Ala Pro Pro Gly Gly Ala Asp Arg Arg Pro Asn Ala Val Gly Pro Glu			
	210	215	220	
	Arg Gly Ala Gly Thr Ala Gly Gly Gln Gly Glu Glu Arg Ala Gly Gly			
	225	230	235	240
10	Ala Lys Ala Ser Arg Trp Arg Gly Arg Gln Asn Arg Glu Lys Arg Phe			
	245	250	255	
	Thr Phe Val Ile Ala Val Val Ile Gly Val Phe Val Val Cys Trp Phe			
	260	265	270	
15	Pro Phe Phe Phe Thr Tyr Thr Leu Ile Ala Val Gly Cys Pro Val Pro			
	275	280	285	
	Tyr Gln Leu Phe Asn Phe Phe Trp Phe Gly Tyr Cys Asn Ser Ser			
	290	295	300	
	Leu Asn Pro Val Ile Tyr Thr Ile Phe Asn His Asp Phe Arg Arg Ala			
	305	310	315	320
20	Phe Lys Lys Ile Leu Cys Arg Gly Asp Arg Lys Arg Ile Val			
	325	330		
	(2) INFORMATION FOR SEQ ID NO:23:			
	(i) SEQUENCE CHARACTERISTICS:			
25	(A) LENGTH: 321 amino acids			
	(B) TYPE: amino acid			
	(C) STRANDEDNESS: single			
	(D) TOPOLOGY: linear			
	(ii) MOLECULE TYPE: peptide			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:			
30	Leu Leu Thr Ala Leu Val Leu Ser Val Ile Ile Val Leu Thr Ile Ile			
	1	5	10	15
	Gly Asn Ile Leu Val Ile Leu Ser Val Phe Thr Tyr Lys Pro Leu Arg			
	20	25	30	
35	Ile Val Gln Asn Phe Phe Ile Val Ser Ile Ala Val Ala Asp Leu Thr			
	35	40	45	
	Val Ala Leu Leu Val Leu Pro Phe Trp Ala Tyr Ser Ile Leu Gly Arg			
	50	55	60	
	Trp Glu Phe Gly Ile His Leu Cys Lys Leu Trp Leu Thr Cys Asp Val			
	65	70	75	80
40	Leu Cys Cys Thr Ser Ser Ile Leu Asn Leu Cys Ala Ile Ala Leu Asp			
	85	90	95	
	Arg Tyr Trp Ala Ile Thr Asp Pro Ile Asn Tyr Ala Gln Lys Arg Thr			
	100	105	110	
45	Val Gly Arg Val Leu Leu Ile Ser Gly Val Trp Leu Leu Ser Leu			
	115	120	125	
	Leu Ile Ser Ser Pro Pro Leu Ile Gly Trp Asn Asp Trp Pro Asp Glu			

- 76 -

	130	135	140		
	Phe Thr Ser Ala Thr Pro Cys Glu Leu Thr Ser Gln Arg Ile Gly Tyr				
145	150	155	160		
5	Val Ile Tyr Ser Ser Leu Gly Ser Phe Phe Ile Pro Ile Ala Ile Met	165	170	175	
	Arg Ile Val Tyr Ile Glu Ile Phe Val Ala Thr Arg Arg Arg Leu Arg	180	185	190	
	Glu Arg Ala Arg Ala Asn Lys Ile Asn Thr Ile Ala Leu Lys Ser Thr	195	200	205	
10	Glu Leu Glu Pro Met Ala Asn Ser Ser Pro Val Ala Ala Ser Asn Ser	210	215	220	
	Gly Ser Lys Lys Lys Thr Ser Gly Val Asn Gln Phe Ile Glu Glu Lys	225	230	235	240
15	Gln Lys Ile Ser Leu Ser Lys Glu Arg Arg Ala Ala Arg Thr Leu Gly	245	250	255	
	Ile Ile Met Val Phe Val Ile Cys Trp Leu Pro Phe Phe Ile Met Tyr	260	265	270	
	Val Ile Leu Pro Phe Cys Cys Pro Thr Asn Lys Phe Lys Asn Phe Ile	275	280	285	
20	Thr Trp Leu Gly Tyr Ile Asn Ser Gly Leu Asn Pro Val Ile Tyr Thr	290	295	300	
	Ile Phe Asn Leu Asp Tyr Arg Arg Ala Phe Lys Arg Leu Leu Gly Leu	305	310	315	320
25	Asn				

## (2) INFORMATION FOR SEQ ID NO:24:

	(i) SEQUENCE CHARACTERISTICS:				
	(A) LENGTH: 373 amino acids				
30	(B) TYPE: amino acid				
	(C) STRANDEDNESS: single				
	(D) TOPOLOGY: linear				
	(ii) MOLECULE TYPE: peptide				
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:				
35	Arg Ile Leu Thr Ala Cys Phe Leu Ser Leu Leu Ile Leu Ser Thr Leu				
	1	5	10	15	
	Leu Gly Asn Thr Leu Val Cys Ala Ala Val Ile Arg Phe Arg His Leu				
	20	25	30		
	Arg Ser Lys Val Thr Asn Phe Phe Val Ile Ser Leu Ala Val Ser Asp				
	35	40	45		
40	Leu Leu Val Ala Val Leu Leu Trp Lys Ala Val Ala Glu Ile Ala Gly				
	50	55	60		
	Phe Trp Pro Phe Gly Ser Phe Cys Asn Ile Trp Val Ala Phe Asp Ile				
	65	70	75	80	
45	Met Cys Ser Thr Ala Ser Ile Leu Asn Leu Cys Val Ile Ser Val Asp				
	85	90	95		
	Arg Tyr Trp Ala Ile Ser Ser Pro Phe Arg Tyr Glu Arg Lys Lys Arg				

- 77 -

	100	105	110
	Pro Lys Ala Ala Phe Ile Leu Ile Ser Val Ala Trp Thr Leu Ser Val		
	115	120	125
5	Leu Ile Ser Phe Ile Pro Val Gln Leu Ser Trp His Lys Ala Lys Pro		
	130	135	140
	Thr Ser Pro Ser Asp Gly Met Ala Thr Ser Leu Ala Glu Thr Ile Asp		
	145	150	155
	Asn Cys Asp Ser Ser Leu Ser Arg Thr Tyr Ala Ile Ser Ser Val		
	165	170	175
10	Ile Ser Phe Tyr Ile Pro Val Ala Ile Leu Val Thr Tyr Thr Arg Ile		
	180	185	190
	Tyr Arg Ile Ala Gln Lys Gln Ile Arg Arg Ile Ala Ala Leu Glu Arg		
	195	200	205
15	Ala Ala Val His Ala Lys Asn Cys Gln Gly Asn Lys Pro Val Glu Cys		
	210	215	220
	Ser Gln Pro Glu Ser Ser Phe Met Ser Phe Lys Arg Glu Thr Lys Val		
	225	230	235
	Leu Lys Thr Leu Ser Val Ile Thr Cys Val Phe Val Cys Cys Trp Leu		
	245	250	255
20	Pro Phe Phe Ile Leu Asn Cys Ile Leu Pro Phe Cys Gly Ser Gly Glu		
	260	265	270
	Thr Gln Pro Phe Cys Thr Asp Ser Asn Thr Phe Asp Val Phe Val Trp		
	275	280	285
25	Phe Gly Trp Ala Asn Ser Ser Leu Asn Pro Ile Ile Tyr Ala Phe Asn		
	290	295	300
	Ala Asp Phe Arg Lys Ala Phe Ser Thr Leu Leu Gly Cys Tyr Arg Leu		
	305	310	315
	Cys Pro Ala Thr Asn Met Ala Ile Glu Thr Val Ser Ile Asn Asn Gly		
	325	330	335
30	Ala Ala Met Phe Ser Ser His His Glu Pro Arg Gly Ser Ile Ser Lys		
	340	345	350
	Glu Cys Asn Leu Val Tyr Leu Ile Pro His Ala Val Gly Ser Ser Glu		
	355	360	
	365		
35	Asp Leu Lys Lys Glu		
	370		

## (2) INFORMATION FOR SEQ ID NO:25:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 360 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Gln Trp Thr Ala Cys Leu Leu Thr Leu Leu Ile Ile Trp Thr Leu Leu

1 5 10 15

Gly Asn Val Leu Val Cys Ala Ala Ile Val Arg Ser Arg His Leu Leu

20

25

30

- 78 -

	Val Phe Ile Val Ser Ile Ala Val Ser Asp Leu Phe Val Ala Leu Leu			
	35	40	45	
	Val Asn Thr Trp Lys Ala Tyr Ala Glu Val Ala Gly Tyr Trp Pro Phe			
	50	55	60	
5	Gly Ala Phe Cys Asp Val Trp Val Ala Phe Asp Ile Met Cys Ser Thr			
	65	70	75	80
	Ala Ser Ile Leu Asn Leu Cys Val Ile Ser Val Asp Arg Tyr Trp Ala			
	85	90	95	
10	Ile Ser Arg Pro Phe Arg Tyr Lys Ala Leu Val Met Val Gly Ile Ala			
	100	105	110	
	Trp Thr Leu Ser Ile Leu Ile Ser Phe Ile Pro Val Gln Ile Asn Trp			
	115	120	125	
	Asn Arg Asp Gln Ala Ala Ser Trp Gly Gly Leu Asp Leu Pro Asn Asn			
	130	135	140	
15	Ile Asp Cys Asp Ser Ser Leu Asn Arg Thr Tyr Ala Ile Ser Ser Ser			
	145	150	155	160
	Leu Ile Ser Phe Tyr Ile Pro Val Ala Ile Leu Val Thr Tyr Thr Arg			
	165	170	175	
20	Ile Tyr Arg Ile Ala Gln Val Gln Ile Arg Arg Ile Ser Ser Leu Glu			
	180	185	190	
	Arg Ala Ala Glu His Ala Gln Ser Cys Arg Ser Ser Ala Ala Cys Ala			
	195	200	205	
	Pro Asp Thr Ser Leu Arg Ala Ser Ile Lys Lys Glu Thr Lys Val Leu			
	210	215	220	
25	Lys Thr Leu Ser Val Ile Ile Cys Val Phe Val Cys Cys Trp Leu Pro			
	225	230	235	240
	Phe Phe Ile Leu Asn Cys Met Val Pro Phe Cys Ser Gly His Pro Glu			
	245	250	255	
30	Gly Pro Pro Ala Gly Phe Pro Cys Val Ser Glu Thr Thr Phe Asp Val			
	260	265	270	
	Phe Val Trp Phe Gly Trp Ala Asn Ser Ser Leu Asn Pro Val Ile Tyr			
	275	280	285	
	Ala Phe Asn Ala Asp Phe Gln Lys Val Phe Ala Gln Leu Leu Cys Ser			
	290	295	300	
35	His Phe Cys Ser Arg Thr Pro Val Glu Thr Val Asn Ile Ser Asn Glu			
	305	310	315	320
	Leu Ile Ser Tyr Asn Gln Asp Ile Val Phe His Lys Glu Ile Ala Ala			
	325	330	335	
40	Ala Tyr Ile His Met Met Pro Asn Ala Val Thr Pro Gly Asn Arg Glu			
	340	345	350	
	Val Asp Asn Asp Glu Glu Gly			
	355	360		

## (2) INFORMATION FOR SEQ ID NO:26:

## (i) SEQUENCE CHARACTERISTICS:

- 45 (A) LENGTH: 314 amino acids  
 (B) TYPE: amino acid

- 79 -

(C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

5	Tyr Asn Tyr Tyr Ala Thr Leu Leu Thr Leu Leu Ile Ala Va. Ile Val
	1                       5                       10                       15
	Phe Gly Asn Val Leu Val Cys Met Ala Val Ser Arg Glu Lys Ala Leu
	20                      25                      30
10	Gln Thr Met Asn Tyr Leu Ile Val Ser Ile Ala Val Ala Asp Leu Leu
	35                      40                      45
	Val Ala Thr Leu Val Trp Trp Trp Tyr Leu Glu Val Val Gly Glu Trp
	50                      55                      60
	Lys Phe Ser Arg Ile His Cys Asp Ile Phe Val Thr Leu Asp Ile Thr
	65                      70                      75                      80
15	Ala Ser Ile Leu Asn Leu Cys Ala Ile Ser Ile Asp Arg Tyr Thr Ala
	85                      90                      95
	Val Ala Met Pro Met Leu Tyr Asn Thr Arg Tyr Ser Ser Lys Arg Arg
	100                    105                    110
20	Val Thr Val Met Ile Ser Ile Val Trp Val Leu Ser Phe Thr Ile Ser
	115                    120                    125
	Cys Pro Leu Leu Phe Gly Leu Asn Asn Ala Asp Gln Asn Glu Cys Ile
	130                    135                    140
	Ile Ala Asn Pro Ala Phe Val Val Tyr Ser Ser Ile Val Se. Phe Tyr
	145                    150                    155                    160
25	Val Pro Phe Ile Val Thr Leu Leu Val Tyr Ile Lys Ile Tyr Ile Val
	165                    170                    175
	Leu Arg Arg Arg Lys Arg Val Asn Thr Lys Arg Ser Ser Arg Ala
	180                    185                    190
30	Phe Arg Ala His Leu Arg Ala Pro Leu Lys Gly Asn Cys Thr His Pro
	195                    200                    205
	Glu Asp Met Lys Leu Cys Thr Val Ile Pro Asn Gly Lys Thr Arg Thr
	210                    215                    220
	Ser Leu Lys Thr Met Ser Arg Arg Lys Leu Ser Gln Gln Lys Glu Lys
	225                    230                    235                    240
35	Lys Ala Thr Gln Met Ile Ala Ile Val Leu Gly Val Phe Ile Ile Cys
	245                    250                    255
	Lys Leu Pro Phe Phe Ile Thr His Ile Leu Asn Ile His Cys Asp Cys
	260                    265                    270
40	Asn Ile Pro Pro Val Leu Tyr Ser Ala Phe Thr Trp Leu Gly Tyr Val
	275                    280                    285
	Asn Ser Ala Val Asn Pro Ile Ile Tyr Thr Phe Asn Ile Glu Phe
	290                    295                    300

---

Arg Lys Ala Phe Leu Lys Ile Leu His Cys  
305                    310

45 (2) INFORMATION FOR SEQ ID NO:27:  
 (i) SEQUENCE CHARACTERISTICS:

- 80 -

- (A) LENGTH: 317 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Ala	Tyr	Tyr	Ala	Leu	Ser	Tyr	Cys	Ala	Leu	Ile	Leu	Ala	Ile	Val	Phe
1				5					10				15		

Gly	Asn	Gly	Leu	Val	Cys	Met	Ala	Val	Leu	Arg	Glu	Lys	Ala	Leu	Gln
10				20		25				30					

Thr	Thr	Thr	Asn	Tyr	Leu	Val	Val	Ser	Leu	Ala	Val	Ala	Asp	Leu	Leu
35					40					45					

Val	Ala	Thr	Leu	Val	Trp	Trp	Val	Val	Tyr	Leu	Glu	Val	Thr	Gly	Gly
50					55			60							

15	Val	Trp	Asn	Phe	Ser	Arg	Ile	Cys	Cys	Asp	Val	Phe	Val	Thr	Leu	Asp
65				70			75			80						

Val	Met	Met	Thr	Ala	Ser	Ile	Leu	Asn	Leu	Cys	Ala	Ile	Ser	Ile	Asp
85					90					95					

20	Arg	Tyr	Thr	Ala	Val	His	Tyr	Gln	His	Gly	Thr	Gly	Gln	Ser	Ser	Cys
				100			105		110							

Arg	Arg	Val	Ala	Ile	Met	Ile	Thr	Ala	Val	Trp	Val	Leu	Ala	Phe	Ala
115					120					125					

Val	Ser	Cys	Pro	Leu	Leu	Phe	Gly	Phe	Asn	Thr	Gly	Asp	Pro	Thr	Val
130				135			140								

25	Cys	Ser	Ile	Ser	Asn	Pro	Asp	Phe	Val	Ile	Tyr	Ser	Ser	Val	Val	Ser
145					150			155		160						

Phe	Tyr	Leu	Pro	Phe	Gly	Val	Thr	Val	Leu	Val	Tyr	Ala	Arg	Ile	Tyr
165					170					175					

30	Val	Val	Leu	Lys	Gln	Arg	Arg	Arg	Lys	Arg	Ile	Leu	Thr	Arg	Gln	Asn
				180				185		190						

Ser	Gln	Cys	Asn	Ser	Val	Arg	Pro	Gly	Phe	Pro	Gln	Gln	Ser	Thr	Ser
195					200				205						

Leu	Pro	Asp	Pro	Ala	His	Leu	Glu	Leu	Lys	Arg	Ser	Asn	Gly	Arg	Leu
210				215			220								

35	Ser	Thr	Ser	Leu	Lys	Leu	Pro	Leu	Gln	Pro	Arg	Gly	Val	Pro	Leu	Arg
225					230			235		240						

Glu	Lys	Lys	Ala	Thr	Gln	Met	Val	Ala	Ile	Val	Leu	Gly	Ala	Phe	Ile
245					250			255							

40	Val	Cys	Trp	Leu	Pro	Phe	Phe	Leu	Thr	His	Val	Ile	Asn	Thr	His	Cys
				260			265		270							

Gln	Thr	Cys	His	Val	Ser	Pro	Glu	Leu	Tyr	Ser	Ala	Thr	Thr	Trp	Leu
275					280			285							

Gly	Tyr	Val	Asn	Ser	Ala	Leu	Asn	Pro	Val	Ile	Tyr	Thr	Thr	Phe	Asn
290				295				300							

45	Ile	Glu	Phe	Arg	Lys	Ala	Phe	Leu	Lys	Ile	Leu	Ser	Cys		
				305			310		315						

- 81 -

## (2) INFORMATION FOR SEQ ID NO:28:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 315 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

	Gly Ala Ala Ala Leu Val Gly Gly Val Leu Leu Ile Cys Ala Val Leu
10	1 5 10 15
	Ala Gly Asn Ser Leu Val Cys Val Ser Val Ala Thr Glu Arg Ala Leu
	20 25 30
	Gln Thr Pro Thr Asn Ser Phe Ile Val Ser Leu Ala Ala Ala Asp Leu
	35 40 45
15	Leu Leu Ala Leu Leu Val Leu Pro Leu Phe Val Tyr Ser Glu Val Gln
	50 55 60
	Gly Ala Ala Trp Leu Leu Ser Pro Arg Leu Cys Asp Val Met Leu Cys
	65 70 75 80
20	Thr Ala Ser Ile Phe Asn Leu Cys Ala Ile Ser Val Asp Ar Phe Val
	85 90 95
	Ala Val Ala Val Pro Leu Arg Tyr Asn Arg Gln Gly Gly Ser Arg Arg
	100 105 110
	Gln Leu Leu Leu Ile Gly Ala Thr Trp Leu Leu Ser Ala Ala Val Ala
	115 120 125
25	Ala Pro Val Leu Cys Gly Leu Asn Asp Val Arg Gly Arg Asp Pro Ala
	130 135 140
	Val Cys Arg Leu Glu Asp Arg Asp Tyr Val Val Tyr Ser Ser Val Cys
	145 150 155 160
30	Ser Phe Phe Leu Pro Cys Pro Leu Leu Tyr Trp Ala Thr Phe Arg Gly
	165 170 175
	Leu Gln Leu Val Ala Arg Arg Ala Lys Leu His Gly Arg Ala Pro Arg
	180 185 190
	Arg Pro Ser Gly Pro Gly Pro Pro Ser Pro Thr Pro Pro Ala Pro Arg
	195 200 205
35	Leu Pro Gln Asp Pro Cys Gly Ala Leu Pro Pro Gln Thr Pro Pro Gln
	210 215 220
	Thr Arg Arg Arg Arg Ala Lys Ile Thr Gly Arg Glu Arg Lys Ala
	225 230 235 240
40	Met Arg Val Leu Pro Val Val Val Gly Ala Phe Ile Leu Cys Trp Thr
	245 250 255
	Pro Phe Phe Val Val His Ile Thr Gln Ala Leu Cys Pro Ala Cys Ser
	260 265 270
	<del>Val Pro Pro Arg Leu Val Ser Ala Val Thr Trp Leu Ser Tyr Val Asn</del>
	275 280 285
45	Ser Ala Ile Asn Pro Val Ile Tyr Thr Val Phe Asn Ala Glu Phe Arg
	290 295 300
	Asn Val Phe Arg Lys Ala Leu Arg Ala Cys Cys

- 82 -

305 310 315

## (2) INFORMATION FOR SEQ ID NO:29:

## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 327 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

10 Lys Ile Ser Leu Ala Val Val Leu Ser Val Ile Thr Leu Ala Thr Val  
 1 5 10 15

Leu Ser Asn Ala Phe Val Leu Thr Arg Ile Leu Leu Thr Arg Lys Leu  
 20 25 30

15 His Thr Pro Ala Asn Tyr Leu Ile Gly Ser Ile Ala Thr Thr Asp Leu  
 35 40 45

Leu Val Ser Ile Leu Val Trp Ile Ser Ile Ala Tyr Thr Ile Thr His  
 50 55 60

Thr Trp Asn Phe Gly Gln Ile Leu Cys Asp Ile Trp Leu Ser Ser Asp  
 65 70 75 80

20 Ile Thr Cys Cys Thr Ala Ser Ile Leu His Leu Cys Val Ile Ala Leu  
 85 90 95

Asp Arg Tyr Trp Ala Ile Thr Asp Ala Leu Glu Tyr Ser Lys Arg Arg  
 100 105 110

25 Thr Ala Gly His Ala Ala Thr Met Ile Ala Ile Val Trp Ala Ile Ser  
 115 120 125

Ile Cys Ile Ser Ile Pro Pro Leu Phe Trp Arg Ala Lys Ala Gln Glu  
 130 135 140

Glu Met Ser Asp Cys Leu Val Asn Thr Ser Gln Ser Tyr Thr Ile Tyr  
 145 150 155 160

30 Ser Thr Cys Gly Ala Phe Tyr Ile Pro Ser Val Leu Leu Ile Ile Leu  
 165 170 175

Tyr Gly Arg Ile Tyr Arg Ala Ala Arg Asn Arg Ile Leu Asn Pro Pro  
 180 185 190

35 Ser Leu Tyr Gly Lys Arg Phe Thr Thr Ala His Leu Ile Thr Gly Ser  
 195 200 205

Ala Gly Ser Ser Leu Cys Ser Leu Asn Ser Ser Leu His Glu Gly His  
 210 215 220

Asn His Val Lys Ile Lys Leu Ala Asp Ser Ala Leu Glu Arg Lys Arg  
 225 230 235 240

40 Ile Ser Ala Ala Arg Glu Arg Lys Ala Thr Lys Ile Leu Gly Ile Ile  
 245 250 255

Leu Gly Ala Phe Ile Ile Cys Trp Leu Pro Phe Phe Val Val Ser Leu  
 260 265 270

45 Val Leu Pro Ile Cys Arg Asp Ser Cys Trp Ile His Pro Ala Leu Phe  
 275 280 285

Asp Phe Phe Thr Trp Leu Gly Tyr Ile Asn Ser Leu Ile Asn Pro Ile  
 290 295 300

- 83 -

Ile Tyr Thr Val Phe Asn Glu Glu Phe Arg Gln Ala Phe Gln Lys Ile  
 305                   310                   315                   320

Val Pro Phe Arg Lys Ala Ser  
 325

5 (2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 325 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Val Ile Thr Ser Leu Leu Leu Gly Thr Leu Ile Phe Cys Ala Val Leu  
 1                   5                   10                   15

15 Gly Asn Ala Cys Val Val Ala Ala Ile Ala Leu Glu Arg Ser Leu Gln  
 20                   25                   30

Asn Val Ala Asn Tyr Leu Ile Gly Ser Leu Ala Val Arg Asp Leu Met  
 35                   40                   45

20 Val Ser Val Leu Val Leu Pro Met Ala Ala Leu Tyr Gln Val Leu Asn  
 50                   55                   60

Lys Trp Thr Leu Gly Gln Val Thr Cys Asp Leu Phe Ile Ala Leu Asp  
 65                   70                   75                   80

Val Leu Cys Cys Thr Ser Ser Ile Leu His Leu Cys Ala Ile Ala Leu  
 85                   90                   95

25 Asp Arg Tyr Trp Ala Ile Thr Asp Pro Ile Asp Tyr Val Asp Lys Arg  
 100                 105                 110                 115

Thr Pro Arg Pro Arg Ala Leu Ile Ser Leu Thr Trp Leu Ile Gly Phe  
 115                 120                 125

30 Leu Ile Ser Ile Pro Pro Met Leu Gly Trp Arg Thr Pro Glu Asp Arg  
 130                 135                 140

Ser Asp Pro Asp Ala Cys Thr Ile Ser Lys Asp His Gly Tyr Thr Ile  
 145                 150                 155                 160

Tyr Ser Thr Ile Phe Ala Phe Tyr Ile Pro Leu Leu Leu Met Leu Val  
 165                 170                 175

35 Leu Tyr Gly Arg Ile Phe Arg Ala Ala Arg Phe Arg Ile Arg Lys Thr  
 180                 185                 190

Val Lys Lys Val Glu Lys Thr Gly Ala Asp Thr Arg His Gly Ala Ser  
 195                 200                 205

40 Pro Ala Pro Gln Pro Lys Lys Ser Val Asn Gly Glu Ser Gly Ser Arg  
 210                 215                 220

Asn Ala Ser Phe Glu Arg Lys Asn Glu Arg Asn Ala Phe Ala Lys Leu  
 225                 230                 235                 240

~~Leu Ala Arg Glu Arg Lys Thr Val Lys Thr Leu Gly Ile Ile Met Thr~~  
 245                 250                 255

45 Phe Ile Leu Cys Trp Leu Pro Phe Phe Ile Val Ala Leu Val Leu Pro  
 260                 265                 270

Phe Cys Glu Ser Ser Cys His Met Pro Thr Leu Ile Arg Ala Ile Ile

- 84 -

275

280

285

Asn Trp Leu Cys Val Ile Asn Ser Leu Leu Asn Pro Val Ile Tyr Ala  
 290 295 300

5 Tyr Phe Asn Lys Asp Phe Gln Asn Ala Phe Lys Lys Ile Ile Lys Cys  
 305 310 315 320

Asn Phe Cys Arg Gln  
 325

## (2) INFORMATION FOR SEQ ID NO:31:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 385 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Gln Asn Trp Pro Ala Leu Ser Ile Val Val Ile Ile Asn Thr Ile  
 1 5 10 15

Gly Gly Asn Ile Leu Val Ile Met Ala Val Ser Lys Lys Leu His Asn  
 20 25 30

20 Ala Thr Asn Tyr Phe Leu Met Ser Ile Ala Ile Ala Asp Me. Leu Val  
 35 40 45

Gly Phe Leu Val Trp Leu Ser Leu Leu Ala Ile Leu Tyr Asp Tyr Val  
 50 55 60

25 Trp Pro Leu Pro Arg Tyr Leu Cys Pro Val Trp Ile Ser Leu Asp Val  
 65 70 75 80

Leu Phe Ser Thr Ala Ser Ile Met His Leu Cys Ala Ile Ser Leu Asp  
 85 90 95

Arg Tyr Val Ala Ile Arg Asn Pro Ile Glu His Ser Arg Phe Ser Arg  
 100 105 110

30 Thr Lys Ala Ile Met Lys Ile Ala Ile Val Trp Ala Ile Ser Ile Gly  
 115 120 125

Val Ser Val Pro Ile Pro Val Ile Gly Leu Arg Asp Glu Ser Lys Val  
 130 135 140

35 Phe Val Asn Asn Thr Thr Ile Cys Val Leu Asn Asp Pro Asn Phe Val  
 145 150 155 160

Leu Ile Gly Ser Phe Val Ala Phe Phe Ile Pro Thr Leu Ile Met Val  
 165 170 175

Ile Thr Tyr Phe Leu Thr Ile Tyr Val Leu Arg Arg Gln Th. Leu Met  
 180 185 190

40 Leu Leu Arg Gly His Thr Glu Glu Glu Ile Ala Met Ser Leu Asn Phe  
 195 200 205

Leu Asn Cys Cys Cys Lys Lys Asn Gly Gly Glu Glu Asn Ala Pro  
 210 215 220

45 Asn Asn Pro Asn Pro Asp Gln Lys Pro Arg Arg Lys Lys Lys Glu Lys  
 225 230 235 240

Arg Pro Arg Gly Thr Met Gln Ala Ile Asn Asn Glu Lys Lys Ala Ser  
 245 250 255

- 85 -

	Lys Val Leu Gly Ile Val Phe Phe Val Phe Leu Ile Met Trp Cys Pro
	260 265 270
	Phe Phe Ile Thr Asn Ile Leu Ser Val Leu Cys Gly Lys Ala Cys Asn
	275 280 285
5	Gln Cys Lys Leu Leu Asn Val Phe Val Trp Ile Gly Tyr Val Cys Ser
	290 295 300
	Gly Ile Asn Pro Val Ile Tyr Thr Leu Phe Asn Lys Ile Tyr Arg Arg
	305 310 320
10	Ala Phe Ser Lys Tyr Leu Arg Cys Asp Tyr Lys Pro Asp Lys Lys Pro
	325 330 335
	Pro Val Arg Gln Ile Pro Arg Val Ala Ala Thr Ala Leu Ser Gly Arg
	340 345 350
	Glu Leu Asn Val Asn Ile Tyr Arg His Thr Asn Glu Arg Val Ala Arg
	355 360 365
15	Lys Ala Asn Asp Pro Glu Pro Gly Ile Glu Asn Gln Val Glu Asn Leu
	370 375 380
	Glu
	385

20	(2) INFORMATION FOR SEQ ID NO:32:
	(i) SEQUENCE CHARACTERISTICS:
	(A) LENGTH: 379 amino acids
	(B) TYPE: amino acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear
25	(ii) MOLECULE TYPE: peptide
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:
	Lys Asn Trp Ser Ala Leu Leu Thr Thr Val Val Ile Ile Leu Thr Ile
	1 5 10 15
30	Ala Gly Asn Ile Leu Val Ile Met Ala Val Ser Leu Glu Lys Lys Leu
	20 25 30
	Gln Asn Ala Thr Asn Tyr Phe Leu Met Ser Leu Ala Ile Ala Asp Met
	35 40 45
	Leu Leu Gly Phe Leu Val Trp Val Ser Asn Glu Thr Ile Leu Tyr Gly
	50 55 60
35	Tyr Arg Trp Pro Leu Pro Ser Lys Leu Cys Ala Ile Trp Ile Tyr Leu
	65 70 75 80
	Asp Val Leu Phe Ser Thr Ala Ser Ile Met His Leu Cys Ala Ile Ser
	85 90 95
40	Leu Asp Arg Tyr Val Ala Ile Gln Asn Pro Ile His His Ser Arg Phe
	100 105 110
	Asn Ser Arg Thr Lys Ala Phe Leu Lys Ile Ile Ala Val Trp Thr Ile
	115 120 125
	Ser Val Gly Ile Ser Met Pro Ile Pro Val Phe Gly Leu Gln Asp Asp
	130 135 140
45	Ser Lys Val Phe Lys Glu Gly Ser Cys Leu Leu Ala Asp Asp Asn Phe
	145 150 155 160

- 86 -

Val Leu Ile Gly Ser Phe Val Ala Phe Phe Ile Pro Leu Thr Ile Met  
 165 170 175

Val Ile Thr Tyr Phe Leu Thr Ile Lys Ser Leu Arg Gln Lys Phe Ala  
 180 185 190

5 Thr Leu Cys Val Ser Asp Leu Ser Thr Arg Ala Lys Leu Ala Ser Phe  
 195 200 205

Ser Phe Leu Pro Gln Ser Ser Leu Ser Ser Glu Lys Leu Phe Gln Arg  
 210 215 220

10 Ser Ile His Arg Glu Pro Gly Ser Tyr Ala Gly Arg Lys Thr Met Gln  
 225 230 235 240

Ser Ile Ser Asn Glu Gln Lys Ala Cys Lys Val Leu Gly Ile Val Phe  
 245 250 255

Phe Leu Phe Val Val Met Trp Cys Pro Phe Phe Ile Thr Asn Ile Met  
 260 265 270

15 Val Ile Cys Lys Glu Ser Cys Asn Glu Asn Val Ile Gly Ala Leu Leu  
 275 280 285

Asn Val Phe Val Trp Ile Gly Tyr Leu Ser Ser Ala Val Asn Pro Leu  
 290 295 300

20 Val Tyr Thr Leu Phe Asn Lys Thr Tyr Arg Ser Ala Phe Ser Arg Tyr  
 305 310 315 320

Leu Gln Cys Gln Tyr Lys Glu Asn Arg Lys Pro Leu Leu Ile Leu Val  
 325 330 335

Asn Thr Ile Pro Ala Leu Ala Tyr Lys Ser Ser Gln Leu Gln Val Gly  
 340 345 350

25 Gln Lys Lys Asn Ser Gln Glu Asp Ala Glu Gln Thr Val Asp Asp Cys  
 355 360 365

Ser Met Val Thr Leu Gly Lys Gln Gln Ser Glu  
 370 375

(2) INFORMATION FOR SEQ ID NO:33:  
 30 (i) SEQUENCE CHARACTERISTICS:  
     (A) LENGTH: 337 amino acids  
     (B) TYPE: amino acid  
     (C) STRANDEDNESS: single  
     (D) TOPOLOGY: linear  
 35 (iii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:  
 Ile Thr Ile Thr Val Val Leu Ala Val Leu Ile Leu Ile Thr Val Ala  
 1 5 10 15

40 Gly Asn Val Val Val Cys Ile Ala Val Gly Ile Asn Arg Arg Leu Arg  
 20 25 30

Asn Leu Thr Asn Cys Phe Ile Val Ser Leu Ala Ile Thr Asp Leu Leu  
 35 40 45

Leu Gly Leu Leu Val Leu Pro Phe Ser Ala Ile Tyr Gln Leu Ser Cys  
 50 55 60

45 Lys Trp Ser Phe Gly Lys Val Phe Cys Asn Ile Tyr Thr Ser Leu Asp  
 65 70 75 80

Val Met Leu Cys Thr Ala Ser Ile Leu Asn Leu Ile Ser Leu Asp

- 87 -

85

90

95

	Arg Tyr Cys Ala Val Met Asp Pro Leu Arg Tyr Pro Val Leu Val Arg			
	100	105	110	
5	Pro Val Arg Val Ala Ile Ser Leu Val Leu Ile Trp Val Ile Ser Ile			
	115	120	125	
	Thr Leu Ser Phe Leu Ser Ile His Leu Gly Trp Asn Ser Arg Asn Glu			
	130	135	140	
	Thr Ser Lys Gly Asn His Thr Thr Ser Lys Cys Lys Val Gln Val Asn			
10	145	150	155	160
	Glu Val Tyr Gly Leu Val Asp Gly Leu Val Thr Phe Tyr Leu Pro Leu			
	165	170	175	
	Leu Ile Met Cys Ile Thr Tyr Tyr Arg Ile Phe Lys Val Ala Arg Asp			
	180	185	190	
15	Ala Lys Arg Asn His Ile Ser Ser Trp Lys Ala Ala Thr Ile Arg Glu			
	195	200	205	
	His Lys Ala Thr Val Thr Ile Ala Ala Val Met Ala Phe Ile Ile Cys			
	210	215	220	
	Trp Phe Pro Tyr Phe Thr Ala Phe Val Tyr Arg Gly Leu Arg Gly Asp			
	225	230	235	240
20	Asp Ala Ile Asn Glu Val Leu Glu Ala Ile Val Leu Trp Leu Gly Tyr			
	245	250	255	
	Ala Asn Ser Ala Leu Asn Pro Ile Leu Tyr Ala Ala Leu Asn Arg Asp			
	260	265	270	
25	Phe Arg Thr Gly Tyr Gln Gln Leu Phe Cys Cys Arg Ile Ala Asn Arg			
	275	280	285	
	Asn Ser His Lys Thr Ser Leu Arg Ser Asn Ala Ser Gln Leu Ser Arg			
	290	295	300	
	Thr Gln Ser Arg Glu Pro Arg Gln Gln Glu Glu Lys Pro Leu Lys Leu			
	305	310	315	320
30	Gln Val Trp Ser Gly Thr Glu Val Thr Ala Pro Gln Gly Ala Thr Asp			
	325	330	335	
	Arg			

## (2) INFORMATION FOR SEQ ID NO:34:

- 35      (i) SEQUENCE CHARACTERISTICS:  
         (A) LENGTH: 315 amino acids  
         (B) TYPE: amino acid  
         (C) STRANDEDNESS: single  
         (D) TOPOLOGY: linear
- 40      (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Ile	Ile	Thr	Tyr	Leu	Val	Phe	Ala	Val	Arg	Phe	Val	Leu	Gly	Val	Leu
1	5														

Gly	Asn	Gly	Leu	Val	Ile	Trp	Val	Ala	Gly	Phe	Arg	Met	Thr	His	Thr
20									25				30		

Val	Thr	Thr	Ile	Ser	Tyr	Leu	Asn	Leu	Ala	Val	Ala	Asp	Phe	Cys	Phe
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

- 88 -

	35	40	45
	Thr Ser Thr Leu Pro Phe Phe Met Val Arg Leu Gly His Trp Pro Phe		
	50	55	60
5	Gly Trp Phe Leu Cys Lys Phe Leu Phe Thr Ile Val Asp Ile Asn Leu		
	65	70	75
	Phe Gly Ser Val Phe Leu Ile Ala Leu Ile Ala Leu Asp Arg Cys Val		
	85	90	95
	Cys Val Leu His Pro Val Trp Thr Gln Asn His Arg Thr Val Ser Leu		
	100	105	110
10	Ala Lys Lys Val Ile Ile Gly Pro Trp Val Met Ala Leu Leu Leu Thr		
	115	120	125
	Leu Pro Val Ile Ile Arg Val Thr Ile Val Pro Gly Lys Thr Gly Thr		
	130	135	140
15	Val Ala Cys Thr Phe Asn Phe Ser Pro Trp Thr Asn Asp Pro Lys Glu		
	145	150	155
	Arg Ile Asn Val Ala Val Ala Met Leu Thr Val Arg Gly Ile Ile Arg		
	165	170	175
	Phe Ile Ile Gly Phe Ser Ala Pro Met Ser Ile Val Ala Val Ser Tyr		
	180	185	190
20	Gly Leu Ile Ala Thr Lys Ile Ile Lys Ser Ser Arg Pro Leu Arg Val		
	195	200	205
	Leu Ser Phe Val Ala Ala Ala Phe Phe Leu Cys Trp Ser Pro Tyr Gln		
	210	215	220
25	Val Val Ala Leu Ile Ala Thr Val Arg Ile Arg Glu Leu Leu Gln Gly		
	225	230	235
	Met Tyr Lys Glu Ile Gly Ile Ala Val Asp Val Thr Ser Ala Ile Ala		
	245	250	255
	Phe Phe Asn Ser Cys Leu Asn Pro Leu Tyr Val Phe Met Gly Gln Asp		
	260	265	270
30	Phe Arg Glu Arg Leu Ile His Ala Leu Pro Ala Ser Leu Glu Arg Ala		
	275	280	285
	Leu Thr Glu Asp Ser Thr Gln Thr Ser Asp Thr Ala Thr Asn Ser Thr		
	290	295	300
35	Leu Pro Ser Ala Glu Val Ala Leu Gln Ala Lys		
	305	310	315

## (2) INFORMATION FOR SEQ ID NO:35:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 304 amino acids
- (B) TYPE: amino acid

40 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

45 Asp Ile Leu Ala Leu Val Ile Phe Ala Val Val Phe Leu Val Gly Val  
 1 5 10 15

Leu Gly Asn Ala Leu Val Val Trp Val Thr Ala Phe Glu Ala Lys Arg

- 89 -

	20	25	30	
	Thr Ile Asn Ala Ile Trp Phe Leu Asn Ile Ala Val Ala Asp Phe Leu			
	35	40	45	
5	Ser Cys Leu Ala Leu Pro Ile Leu Phe Thr Ser Ile Val Gln His His			
	50	55	60	
	His Trp Pro Phe Gly Gly Ala Ala Cys Ser Ile Leu Pro Ser Leu Ile			
	65	70	75	80
	Leu Leu Asn Met Tyr Ala Ser Ile Leu Leu Ala Thr Ile Ser Ala			
	85	90	95	
10	Asp Arg Phe Leu Leu Val Phe Lys Pro Ile Trp Cys Gln Asn Phe Arg			
	100	105	110	
	Gly Ala Gly Leu Ala Trp Ile Ala Cys Ala Val Ala Trp Gly Ile Ala			
	115	120	125	
15	Leu Leu Leu Thr Ile Pro Ser Phe Leu Tyr Arg Val Val Arg Glu Glu			
	130	135	140	
	Tyr Phe Pro Pro Lys Val Leu Cys Gly Cys Asp Tyr Ser His Asp Lys			
	145	150	155	160
	Arg Arg Glu Arg Ala Val Ala Ile Val Arg Leu Val Leu Gly Phe Leu			
	165	170	175	
20	Trp Pro Leu Leu Thr Leu Thr Ile Cys Tyr Thr Thr Arg Ser Thr Lys			
	180	185	190	
	Thr Leu Lys Val Val Val Ala Val Val Ala Ser Phe Phe Ile Phe Trp			
	195	200	205	
25	Leu Pro Tyr Gln Val Thr Gly Ile Met Met Ser Phe Leu Glu Pro Ser			
	210	215	220	
	Ser Pro Thr Phe Leu Leu Leu Asn Lys Leu Asp Ser Leu Cys Val Ser			
	225	230	235	240
	Phe Ala Tyr Ile Asn Cys Cys Ile Asn Pro Ile Ile Tyr Val Val Ala			
	245	250	255	
30	Gly Gln Gly Gln Phe Gln Gly Arg Leu Arg Lys Ser Leu Pro Ser Leu			
	260	265	270	
	Leu Arg Asn Val Leu Thr Glu Glu Ser Val Val Arg Glu Ser Lys Ser			
	275	280	285	
35	Phe Thr Arg Ser Thr Val Asp Thr Met Ala Gln Lys Thr Gln Ala Val			
	290	295	300	

## (2) INFORMATION FOR SEQ ID NO:36:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 322 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

45	Thr Leu Phe Val Pro Ser Val Tyr Thr Gly Val Phe Val Val Ser Leu		
	1	5	10
	15		

Pro Leu Asn Ile Met Ala Ile Val Val Phe Ile Leu Lys Met Lys Val

- 90 -

20

25

30

	Lys Lys Pro Ala Val His Ile Ala Thr Ala Asp Val Leu Phe Val Ser
	35 40 45
5	Val Leu Pro Phe Lys Ile Ser Tyr Tyr Phe Ser Gly Ser Asp Trp Gln
	50 55 60
	Phe Gly Ser Glu Leu Cys Arg Phe Val Thr Ala Ala Phe Tyr Cys Asn
	65 70 75 80
	Met Tyr Ala Ser Ile Leu Leu Ile Ser Ile Asp Arg Phe Ile Ala Val
	85 90 95
10	Val Tyr Pro Met Gln Ser Leu Ser Trp Arg Thr Leu Gly Arg Ala Ser
	100 105 110
	Phe Thr Cys Ile Ala Ile Trp Ala Ile Ala Ile Ala Gly Val Pro Leu
	115 120 125
15	Val Leu Lys Glu Gln Thr Ile Gln Val Pro Gly Leu Asn Ile Thr Thr
	130 135 140
	Ile Cys His Asp Val Leu Asn Glu Thr Leu Leu Glu Gly Tyr Tyr Ala
	145 150 155 160
	Tyr Tyr Phe Ser Ala Phe Ser Ala Val Phe Phe Phe Val Pro Leu Ile
	165 170 175
20	Ile Ser Thr Val Cys Tyr Val Ser Ile Ile Arg Cys Leu Ser Ser Ser
	180 185 190
	Ala Val Ala Asn Arg Ser Lys Lys Ser Arg Thr Asn Arg Cys Phe Asn
	195 200 205
25	Ser Thr Val Ala Leu Phe Leu Ser Ala Ala Val Phe Cys Ile Phe Ile
	210 215 220
	Ile Cys Phe Gly Pro Thr Trp Leu Leu Ile Ala His Tyr Ser Phe Leu
	225 230 235 240
	Ser His Thr Ser Thr Glu Ala Ala Tyr Phe Ala Tyr Leu Leu Cys
	245 250 255
30	Val Cys Val Ser Ser Ile Ser Ser Cys Ile Asp Pro Leu Ile Tyr Tyr
	260 265 270
	Tyr Ala Ser Ser Glu Cys Gln Arg Tyr Val Tyr Ser Ile Leu Cys Cys
	275 280 285
35	Lys Glu Ser Ser Asp Pro Ser Ser Tyr Asn Ser Ser Gly Gln Leu Met
	290 295 300
	Ser Leu Thr Cys Ser Ser Asn Leu Asn Asn Ser Ile Tyr Lys Lys Leu
	305 310 315 320
	Leu Thr

## 40 (2) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 311 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

45

- 91 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Tyr	Ile	Asn	Thr	Val	Ile	Ser	Cys	Thr	Ile	Phe	Ile	Val	Gly	Trp	Gly	
1															15	
5																
	Asn	Ala	Thr	Leu	Leu	Arg	Ile	Ile	Tyr	Gln	Asn	Lys	Cys	Met	Arg	Asn
							20			25				30		
	Gly	Pro	Asn	Ala	Leu	Ile	Ala	Ser	Ile	Ala	Leu	Gly	Asp	Leu	Ile	Tyr
							35			40				45		
	Val	Val	Ile	Asp	Leu	Pro	Ile	Asn	Val	Pro	Lys	Leu	Ile	Ala	Gly	Arg
							50			55			60			
10																
	Trp	Pro	Phe	Glu	Gln	Asn	Asp	Phe	Gly	Val	Phe	Cys	Lys	Phe	Met	Gly
							65			70		75		80		
	Val	Val	Met	Ile	Phe	Phe	Gly	Leu	Ser	Pro	Leu	Leu	Gly	Ala	Ala	
							85			90			95			
15																
	Met	Ala	Ser	Glu	Arg	Tyr	Leu	Gly	Ile	Thr	Arg	Pro	Phe	Ser	Arg	Pro
							100			105			110			
	Ala	Val	Ala	Ser	Gln	Arg	Arg	Ala	Trp	Ala	Thr	Val	Gly	Leu	Val	Trp
							115			120			125			
	Ala	Ala	Ala	Leu	Ala	Leu	Gly	Leu	Leu	Pro	Leu	Leu	Gly	Val	Gly	Arg
							130			135			140			
20																
	Tyr	Thr	Val	Gln	Tyr	Pro	Gly	Ser	Trp	Cys	Phe	Leu	Thr	Leu	Gly	Ala
							145			150			155			160
	Glu	Ser	Gly	Asp	Val	Ala	Phe	Gly	Leu	Leu	Phe	Ser	Gly	Leu	Ser	Val
							165			170			175			
25																
	Gly	Leu	Ser	Phe	Leu	Leu	Asn	Thr	Val	Ser	Val	Ala	Thr	Leu	His	His
							180			185			190			
	Val	Tyr	His	Gly	Gln	Glu	Ala	Ala	Gln	Gln	Arg	Pro	Arg	Asp	Ser	Glu
							195			200			205			
	Val	Glu	Met	Met	Ala	Gln	Leu	Leu	Gly	Ile	Met	Val	Val	Ala	Ser	Val
							210			215			220			
30																
	Cys	Trp	Leu	Pro	Leu	Leu	Val	Phe	Ile	Ala	Gln	Thr	Val	Leu	Arg	Asn
							225			230			235			240
	Pro	Pro	Ala	Met	Ser	Pro	Ala	Gly	Gln	Leu	Ser	Arg	Thr	Thr	Glu	Lys
							245			250			255			
35																
	Glu	Leu	Leu	Ile	Tyr	Leu	Arg	Val	Ala	Thr	Trp	Asn	Gln	Ile	Leu	Asp
							260			265			270			
	Pro	Trp	Val	Tyr	Ile	Leu	Phe	Arg	Arg	Ala	Val	Leu	Arg	Arg	Leu	Gln
							275			280			285			
	Pro	Arg	Leu	Ser	Thr	Arg	Pro	Arg	Ser	Leu	Ser	Leu	Gln	Pro	Gln	Leu
							290			295			300			
40																
	Thr	Gln	Arg	Ser	Gly	Leu	Gln									
							305			310						

## (2) INFORMATION FOR SEQ ID NO:38:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 312 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

45

- 92 -

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

	Lys	Tyr	Phe	Val	Val	Ile	Ile	Tyr	Ala	Leu	Val	Phe	Leu	Leu	Ser	Leu
1																15
5	Leu	Gly	Asn	Ser	Leu	Val	Met	Leu	Val	Ile	Leu	Tyr	Ser	Arg	Gly	Val
																30
	Arg	Ser	Val	Thr	Ile	Val	Tyr	Leu	Leu	Asn	Ile	Ala	Ile	Ala	Asp	Leu
																45
10	Leu	Phe	Ala	Leu	Thr	Leu	Pro	Ile	Trp	Ala	Ala	Ser	Lys	Val	Asn	Gly
	50						55						60			
	Trp	Ile	Phe	Gly	Thr	Phe	Leu	Cys	Lys	Trp	Ser	Leu	Leu	Lys	Glu	Val
																80
	65						70						75			
	Asn	Phe	Tyr	Ser	Gly	Ile	Leu	Leu	Leu	Ala	Cys	Ile	Ser	Val	Asp	Arg
																95
15	Tyr	Leu	Ala	Ile	Val	Arg	Ala	Thr	Arg	Thr	Leu	Thr	Gln	Lys	Arg	His
																110
							100					105				
	Leu	Val	Lys	Phe	Ile	Cys	Leu	Ser	Ile	Trp	Gly	Leu	Ser	Leu	Leu	Leu
																125
20	115						120									
	Ala	Leu	Pro	Val	Leu	Leu	Phe	Arg	Arg	Thr	Val	Tyr	Ser	Ser	Asn	Val
																140
	130						135									
	Ser	Pro	Ala	Cys	Tyr	Glu	Asp	Met	Gly	Asn	Asn	Tyr	Ala	Asn	Trp	Arg
	145						150						155			160
	Met	Leu	Leu	Pro	Ile	Leu	Pro	Gln	Ser	Phe	Gly	Phe	Ile	Val	Pro	Leu
																175
25	165						170									
	Leu	Ile	Met	Leu	Tyr	Cys	Tyr	Gly	Phe	Thr	Leu	Arg	Thr	Leu	Phe	Lys
																190
	180						185									
	Ala	Ile	Met	Gly	Gln	Lys	His	Arg	Ala	Met	Arg	Val	Ile	Phe	Ala	Val
	195						200									205
30	210						215									
	Val	Leu	Ile	Phe	Leu	Leu	Cys	Trp	Leu	Pro	Tyr	Asn	Leu	Val	Ile	
	220						225									
	Ala	Asp	Thr	Leu	Met	Arg	Thr	Gln	Val	Ile	Gln	Glu	Thr	Cys	Glu	Arg
	225						230						235			240
	Arg	Asn	His	Ile	Asp	Arg	Ala	Ile	Asp	Ala	Thr	Glu	Ile	Leu	Gly	Ile
	245						250									255
35	Leu	His	Ser	Cys	Leu	Asn	Pro	Leu	Ile	Tyr	Ala	Phe	Ile	Gly	Gln	Lys
	260						265									
	Phe	Arg	His	Gly	Leu	Leu	Lys	Ile	Leu	Ala	Ile	His	Gly	Leu	Ile	Ser
	275						280									285
40	290						295									
	Lys	Asp	Ser	Leu	Pro	Lys	Asp	Ser	Arg	Pro	Ser	Phe	Val	Gly	Ser	Ser
																300
	305						310									

## (2) INFORMATION FOR SEQ ID NO:39:

## (i) SEQUENCE CHARACTERISTICS:

- 45 (A) LENGTH: 326 amino acids  
 (B) TYPE: amino acid

- 93 -

(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear  
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Leu Phe Pro Ile Val Tyr Ser Ile Ile Phe Val Leu Gly Ile Ile Ala  
 1 5 10 15

Asn Gly Tyr Val Leu Trp Val Phe Ala Arg Leu Tyr Pro Ser Lys Lys  
 20 25 30

Asn Glu Ile Lys Ile Phe Met Val Asn Leu Thr Val Ala Asp Leu Leu  
 35 40 45

Phe Leu Ile Thr Leu Pro Leu Trp Ile Val Tyr Tyr Ser Asn Gln Gly  
 50 55 60

Asn Trp Phe Leu Pro Lys Phe Leu Cys Asn Leu Ala Gly Cys Leu Phe  
 65 70 75 80

Phe Ile Asn Thr Tyr Cys Ser Val Ala Phe Leu Gly Val Ile Thr Tyr  
 85 90 95

Asn Arg Phe Gln Ala Val Lys Tyr Pro Ile Lys Thr Ala Gln Ala Thr  
 100 105 110

Thr Arg Lys Arg Gly Ile Ala Leu Ser Leu Val Ile Trp Val Ala Ile  
 115 120 125

Val Ala Ala Ala Ser Tyr Phe Leu Val Met Met Asp Ser Thr Asn Val  
 130 135 140

Val Ser Asn Lys Ala Gly Ser Gly Asn Ile Thr Arg Cys Phe Glu Arg  
 145 150 155 160

Tyr Glu Lys Gly Ser Lys Pro Val Leu Ile Ile His Ile Cys Ile Val  
 165 170 175

Leu Gly Phe Phe Ile Val Phe Leu Leu Ile Leu Phe Cys Asn Leu Val  
 180 185 190

Ile Ile His Thr Leu Leu Arg Gly Pro Val Lys Gln Gln Arg Asn Ala  
 195 200 205

Glu Val Arg Arg Arg Ala Leu Trp Met Val Cys Thr Val Ile Ala Val  
 210 215 220

Phe Val Ile Cys Phe Val Pro His His Met Val Gln Leu Pro Trp Thr  
 225 230 235 240

Leu Ala Glu Leu Cys Met Trp Pro Ser Ser Asn His Gln Ala Ile Asn  
 245 250 255

Asp Ala His Gln Val Thr Leu Cys Leu Leu Ser Thr Asn Cys Val Leu  
 260 265 270

Asp Pro Val Ile Tyr Cys Phe Leu Thr Lys Lys Phe Arg Lys His Leu  
 275 280 285

Ser Glu Lys Leu Asn Ile Met Arg Ser Ser Gln Lys Cys Ser Arg Val  
 290 295 300

Thr Arg Asp Thr Gly Thr Glu Met Ala Ile Pro Ile Asn His Thr Pro  
 305 310 315 320

Val Asn Pro Ile Lys Asn

325

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 333 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single

(D) TOPOLOGY: linear  
(ii) MOLECULE TYPE: peptide

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:  
Tyr Ile Asn Thr Ile Val Ser Cys Leu Val Phe Val Leu Gly Ile Ile  
1 5 10 15

Gly Asn Ser Thr Leu Leu Arg Ile Ile Tyr Lys Asn Lys Cys Met Arg  
20 25 30

15 Asn Gly Pro Asn Ile Leu Ile Ala Ser Ile Ala Leu Gly Asp Leu Leu  
35 40 45

His Ile Ile Ile Asp Ile Pro Ile Met Ala Tyr Lys Leu Ile Ala Gly  
50. 55 60

Asp Trp Pro Phe Ala Cys Lys Leu Phe Pro Phe Leu Gln Lys Ser Ser  
65 70 75 80

20 Val Gly Ile Thr Val Leu Asn Leu Cys Ala Leu Ser Val Asp Arg Tyr  
85 90 95

Arg Ala Val Ala Ser Trp Ser Arg Val Gln Gly Ile Gly Ile Pro Leu  
100 105 110

25 Val Thr Ala Ile Glu Ile Val Ser Ile Trp Ile Leu Ser Phe Ile Leu  
           115                 120                 125

Ala Ile Pro Glu Ala Ile Gly Phe Trp Met Val Pro Phe Glu Tyr Lys  
130 135 140

Gly Ala Gln His Arg Thr Cys Met Leu Asn Ala Thr Ser Lys Leu Phe  
145 150 . 155 160

Val Cys Thr Ala Ile Phe Tyr Thr Leu Met Thr Cys Glu Met Leu Asn  
180 185 190

35 Arg Arg Asn Gly Ser Leu Arg Ile Ala Leu Ser Glu His Leu Lys Gln  
           195                   200                   205

Arg Arg Glu Val Ala Lys Thr Val Phe Cys Leu Val Val Ile Phe Ala  
210 215 220

Leu Cys Trp Phe Pro Leu His Leu Ser Arg Ile Leu Lys Lys Thr Val  
225 230 235 240

40 Tyr Asp Glu Met Asp Thr Asn Arg Cys Glu Leu Leu Ser Phe Leu Leu  
245 250 255

Leu Met Tyr Ile Gly Ile Asn Thr Ala Thr Met Ser Cys Ile Asn Pro  
260 265 270

45 Ile Ala Leu Tyr Phe Val Ser Lys Lys Phe Lys Asn Cys Phe Gln Ser  
           . 275                   280                   285

Cys Leu Cys Cys Cys Cys Tyr Gln Ser Lys Ser Ile Met Thr Ser Val  
290 295 300

- 95 -

Pro Met Gln Gly Thr Ser Ile Gln Trp Lys Asn His Glu Gln Asn Asn  
 305                           310                           315                           320

His Asn Thr Glu Arg Ser Ser His Lys Asp Ser Ile Asn  
 325                           330

5 (2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 350 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Leu Ile Ala Ser Pro Trp Phe Ala Ala Ser Phe Cys Val Val Gly Leu  
 1                           5                               10                           15

15 Ala Ser Asn Leu Leu Ala Leu Ser Val Leu Ala Gly Ala Arg Gln Ser  
 20                           25                               30

Ser Ser His Thr Arg Ser Ser Phe Leu Thr Phe Leu Cys Gly Leu Val  
 35                           40                               45

20 Leu Thr Leu Asp Phe Leu Gly Leu Leu Val Thr Gly Thr Ile Val Val  
 50                           55                               60

Ser Gln His Ala Ala Leu Phe Glu Trp His Ala Val Asp Pro Gly Cys  
 65                           70                               75                           80

Arg Leu Cys Arg Leu Val Pro Phe Ile Gln Lys Ala Ser Val Gly Ile  
 85                           90                               95

25 Thr Val Leu Ser Leu Cys Ala Leu Ser Ile Asp Arg Tyr Arg Ala Val  
 100                       105                               110

Ala Ser Trp Ser Arg Ile Lys Gly Ile Gly Val Pro Lys Trp Thr Ala  
 115                       120                               125

30 Val Glu Ile Val Leu Ile Trp Val Val Ser Val Val Leu Ala Val Pro  
 130                       135                               140

Glu Ala Ile Gly Phe Asp Thr Thr Ser Asp Tyr Lys Gly Lys Pro Leu  
 145                       150                               155                           160

Arg Val Cys Met Leu Asn Pro Phe Gln Lys Thr Ala Phe Met Phe Tyr  
 165                       170                               175

35 Lys Thr Ala Ala Lys Asp Trp Trp Leu Phe Ala Phe Tyr Phe Cys Leu  
 180                       185                               190

Pro Leu Ala Ile Thr Ala Ile Phe Tyr Thr Leu Met Thr Cys Glu Met  
 195                       200                               205

40 Leu Arg Lys Lys Ser Gly Met Gln Ile Ala Leu Asn Asp His Leu Lys  
 210                       215                               220

Gln Arg Arg Glu Val Ala Lys Thr Val Phe Cys Leu Val Leu Val Phe  
 225                       230                               235                           240

Ala Leu Cys Trp Leu Pro Leu His Leu Ser Arg Ile Leu Lys Leu Thr  
 245                       250                               255

45 Leu Tyr Asp Gln Ser Asn Pro Gln Arg Cys Glu Leu Leu Ser Phe Leu  
 260                       265                               270

Leu Val Leu Asp Tyr Ile Gly Ile Asn Met Ala Ser Ile Asn Ser Cys

- 96 -

275 280 285

Ile Asn Pro Ile Ala Leu Tyr Leu Val Ser Lys Arg Phe Lys Asn Cys  
 290 295 300

5 Phe Lys Ser Cys Leu Cys Cys Trp Cys Gln Thr Phe Glu Glu Lys Gln  
 305 310 315 320

Ser Leu Glu Glu Lys Gln Ser Cys Leu Lys Phe Lys Ala Asn Asp His  
 325 330 335

Gly Tyr Asp Asn Phe Arg Ser Ser Asn Lys Tyr Ser Ser Ser  
 340 345 350

## 10 (2) INFORMATION FOR SEQ ID NO:42:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 328 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single

15 (D) TOPOLOGY: linear  
 (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Ile Tyr Val Ile Pro Ala Val Tyr Gly Leu Ile Ile Val Ile Gly Leu  
 1 5 10 15  
 20 Ile Gly Asn Ile Thr Leu Ile Lys Ile Phe Cys Thr Val Lys Ser Leu  
 20 25 30

Asn Leu Phe Ile Ser Ser Ile Ala Leu Gly Asp Leu Leu Leu Val  
 35 40 45

25 Thr Ile Cys Ala Pro Val Asp Ala Ser Lys Tyr Ile Ala Asp Arg Trp  
 50 55 60

Leu Phe Gly Arg Ile Gly Cys Lys Leu Ile Pro Phe Ile Gln Leu Thr  
 65 70 75 80

Ser Val Gly Val Ser Val Phe Thr Leu Thr Ala Leu Ser Ala Asp Arg  
 85 90 95

30 Tyr Lys Ala Ile Val Arg Pro Thr Cys Ile Gln Ala Ser Leu Ile Cys  
 100 105 110

Leu Lys Ala Ala Leu Ile Trp Ile Val Ser Leu Leu Ala Ile Pro Glu  
 115 120 125

35 Ala Val Phe Ser Asp Leu His Pro Phe His Val Lys Asp Thr Asn Gln  
 130 135 140

Thr Phe Ile Ser Cys Ala Pro Tyr Pro His Ser Asn Glu Leu His Pro  
 145 150 155 160

Lys Ile His Ser Met Ala Ser Phe Leu Val Phe Tyr Val Ile Pro Leu  
 165 170 175

40 Ala Ile Ile Ser Val Tyr Tyr Phe Ile Ala Arg Asn Leu Ile Gln  
 180 185 190

Ser Ala Tyr Asn Leu Pro Val Glu Gly Asn Ile His Val Lys Lys Gln  
 195 200 205

45 Ile Glu Ser Arg Lys Arg Leu Ala Lys Thr Val Leu Val Phe Val Gly  
 210 215 220

Leu Phe Ala Phe Cys Trp Leu Pro Asn His Val Ile Tyr Leu Tyr Arg  
 225 230 235 240

- 97 -

Ser Tyr His Tyr Ser Glu Val Asp Thr Ser Met Leu His Phe Val Thr  
 245 250 255

Ser Ile Cys Ala Arg Leu Leu Ala Pro Thr Asn Ser Cys Val Asn Pro  
 260 265 270

5 Phe Ala Leu Tyr Leu Leu Ser Lys Ser Phe Arg Gln Phe Asn Thr Gln  
 275 280 285

Leu Leu Cys Cys Gln Pro Gly Leu Ser His Ser Thr Gly Arg Ser Leu  
 290 295 300

10 Ser Phe Lys Ser Thr Asn Pro Ser Ala Thr Phe Ser Leu Ile Asn Arg  
 305 310 315 320

Asn Ile Cys His Glu Gly Tyr Val  
 325

## (2) INFORMATION FOR SEQ ID NO:43:

## (i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 345 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Cys Val Ile Pro Ser Ser Leu Tyr Leu Ile Ile Ile Ser Val Gly Leu  
 1 5 10 15

Leu Gly Asn Ile Met Leu Val Lys Ile Phe Leu Thr Asn Ser Thr Met  
 20 25 30

25 Arg Ser Val Pro Asn Ile Phe Ile Ser Asn Ile Ala Ala Gly Asp Leu  
 35 40 45

Leu Leu Leu Leu Thr Cys Val Pro Val Asp Ala Ser Arg Tyr Phe Phe  
 50 55 60

30 Asp Glu Trp Val Phe Gly Lys Leu Ile Gly Cys Lys Leu Ile Pro Ala  
 65 70 75 80

Ile Gln Leu Thr Ser Val Gly Val Ser Val Pro Thr Leu Thr Ala Leu  
 85 90 95

Ser Ala Asp Arg Tyr Arg Ala Ile Val Asn Pro Met Asp Met Thr Ser  
 100 105 110

35 Gly Val Val Leu Trp Thr Ser Val Ala Val Gly Ile Trp Val Val Ser  
 115 120 125

Val Leu Leu Ala Val Pro Glu Ala Val Phe Ser Glu Val Ala Arg Ile  
 130 135 140

40 Gly Ser Ser Asp Asn Ser Ser Phe Thr Ala Cys Ile Pro Tyr Pro Gln  
 145 150 155 160

Thr Asp Glu Leu His Pro Lys Ile His Ser Val Leu Ile Phe Leu Val  
 165 170 175

Tyr Phe Leu Ile Pro Leu Val Ile Ile Ser Ile Tyr Tyr Tyr His Ile  
 180 185 190

45 Ala Lys Thr Leu Ile Arg Ser Ala His Asn Leu Pro Gly Glu Tyr Asn  
 195 200 205

Glu His Thr Lys Lys Gln Met Glu Thr Arg Lys Arg Leu Ala Lys Ile

- 98 -

	210	215	220	
	Val Leu Val Phe Val Gly Cys Phe Val Phe Cys Trp Phe Pro Asn His			
	225	230	235	240
5	Ile Leu Tyr Leu Tyr Arg Ser Phe Asn Tyr Lys Glu Ile Asp Pro Ser			
	245	250	255	
	Leu Gly Thr Cys Val Thr Leu Val Ala Arg Val Leu Ser Phe Ser Asn			
	260	265	270	
	Ser Cys Val Asn Pro Phe Ala Leu Tyr Leu Leu Ser Glu Ser Phe Arg			
	275	280	285	
10	Lys His Phe Ser Asn Gln Leu Cys Cys Gly Gln Lys Ser Tyr Pro Glu			
	290	295	300	
	Arg Ser Thr Ser Tyr Leu Leu Ser Ser Ser Ala Val Trp Arg Ser Leu			
	305	310	315	320
15	Lys Ser Asn Ala Lys Asn Val Val Thr Asn Ser Val Leu Ile Asn Gly			
	325	330	335	
	His Ser Thr Lys Gln Glu Ile Ala Leu			
	340	345		

## (2) INFORMATION FOR SEQ ID NO:44:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 316 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:			
	Tyr Thr Leu Ser Phe Ile Tyr Ile Phe Ile Phe Val Ile Cys Glx Leu			
	1	5	10	15
25	Leu Ala Asn Ser Val Val Val Trp Val Asn Ile Gln Ala Lys Thr Thr			
	20	25	30	
30	Gly Tyr Asp Thr His Cys Tyr Ile Leu Asn Leu Ala Ile Ala Asp Leu			
	35	40	45	
	Trp Trp Leu Thr Ile Pro Val Trp Trp Ser Leu Val Gln His Asn Gln			
	50	55	60	
35	Trp Pro Met Gly Glu Leu Thr Cys Lys Val Thr His Leu Ile Phe Ser			
	65	70	75	80
	Ile Asn Leu Phe Ser Gly Ile Phe Phe Leu Thr Cys Met Ser Val Asp			
	85	90	95	
	Arg Tyr Leu Ser Ile Thr Tyr Phe Thr Asn Thr Pro Ser Ser Arg Lys			
	100	105	110	
40	Lys Met Val Arg Arg Ala Val Cys Ile Leu Val Trp Leu Leu Ala Phe			
	115	120	125	
	Cys Val Ser Leu Pro Asp Thr Tyr Tyr Leu Lys Thr Val Thr Ser Ala			
	130	135	140	
45	Ser Asn Asn Glu Thr Tyr Cys Arg Ser Phe Tyr Pro Glu His Ser Ile			
	145	150	155	160
	Lys Glu Trp Leu Ile Ser Leu Leu Val Ser Val Val Leu Ile Gly Phe			
	165	170	175	

- 99 -

	Ala Val Pro Phe Ser Ile Ile Ala Val Phe Tyr Phe Ser Leu Ile Ala
	180 185 190
	Arg Ala Ile Ser Ala Ser Ser Asp Gln Glu Lys His Ser Ser Arg Lys
	195 200 205
5	Ile Ile Phe Ser Tyr Val Val Val Phe Leu Val Cys Trp Leu Pro Tyr
	210 215 220
	His Val Ala Val Leu Leu Asp Ile Phe Ser Ile Leu His Tyr Ile Pro
	225 230 235 240
10	Phe Thr Cys Arg Leu Glu His Ala Leu Phe Thr Ala Leu His Val Thr
	245 250 255
	Gln Cys Leu Ser Leu Val His Cys Cys Val Asn Pro Val Leu Tyr Ser
	260 265 270
	Phe Ile Asn Arg Asn Tyr Arg Tyr Glu Ile Asn Trp Ile Phe Lys Tyr
	275 280 285
15	Ser Ala Lys Thr Gly Leu Thr Lys Leu Ile Asp Ala Ser Arg Val Ser
	290 295 300
	Glx Thr Glu Tyr Ser Ala Leu Glu Gln Asn Ala Lys
	305 310 315
20	(2) INFORMATION FOR SEQ ID NO:45:
	(i) SEQUENCE CHARACTERISTICS:
	(A) LENGTH: 353 amino acids
	(B) TYPE: amino acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear
25	(ii) MOLECULE TYPE: peptide
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:
	Lys Val Leu Val Thr Ala Ile Tyr Leu Ala Leu Phe Val Val Gly Thr
	1 5 10 15
30	Val Gly Asn Ser Val Thr Ala Phe Thr Leu Ala Arg Lys Lys Ser Leu
	20 25 30
	Gln Ser Leu Gln Ser Thr Val His Tyr His Leu Ser Ser Leu Ala Leu
	35 40 45
	Ser Asp Leu Leu Ile Leu Leu Trp Val Glu Leu Tyr Asn Phe Ile Trp
	50 55 60
35	His His Pro Trp Ala Phe Gly Asp Ala Gly Cys Arg Gly Tyr Tyr Phe
	65 70 75 80
	Leu Arg Asp Ala Cys Thr Tyr Ala Thr Ala Leu Asn Val Ala Ser Leu
	85 90 95
40	Ser Val Glu Arg Tyr Leu Ala Ile Cys His Pro Phe Lys Ala Lys Thr
	100 105 110
	Leu Met Ser Arg Ser Arg Thr Lys Lys Phe Ile Ser Ala Ile Trp Leu
	115 120 125
	<del>Ala Ser Ala Leu Leu Ala Ile Pro Met Leu Phe Thr Leu Gly Leu Gin</del>
	130 135 140
45	Asn Arg Ser Gly Asp Gly Thr His Pro Gly Gly Leu Val Cys Thr Pro
	145 150 155 160
	Ile Val Asp Thr Ala Thr Val Lys Val Val Ile Gln Val Asn Thr Phe

- 100 -

	165	170	175
	Met Ser Phe Leu Phe Pro Met Leu Val Ile Ser Ile Leu Asn Thr Val		
	180	185	190
5	Ile Ala Asn Lys Leu Thr Val Met Val His Gln Ala Ala Glu Gln Gly		
	195	200	205
	Arg Val Cys Thr Val Gly Thr His Asn Gly Leu Glu His Ser Thr Phe		
	210	215	220
	Asn Met Arg Ile Glu Pro Gly Arg Val Gln Ala Leu Arg His Gly Val		
	225	230	235
10	Leu Val Leu Arg Ala Val Val Ile Ala Phe Val Val Cys Trp Leu Pro		
	245	250	255
	Tyr Leu Cys Tyr Ile Ser Asp Glu Gln Trp Arg Thr Phe Leu Phe Asp		
	260	265	270
15	Phe Tyr His Tyr Phe Tyr Met Leu Thr Asn Ala Leu Phe Tyr Val Ser		
	275	280	285
	Ser Ala Ile Asn Pro Ile Leu Tyr Asn Leu Val Ser Ala Asn Phe Arg		
	290	295	300
	Gln Val Phe Leu Ser Thr Leu Ala Cys Leu Phe Cys Pro Gly Trp Pro		
	305	310	315
20	Leu Ile Arg Arg Lys Lys Arg Pro Thr Phe Ser Arg Lys Pro Asn Ser		
	325	330	335
	Met Ser Ser Asn His Ala Phe Ser Thr Ser Ala Thr Arg Phe Thr Leu		
	340	345	350
25	Tyr		
	(2) INFORMATION FOR SEQ ID NO:46:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 316 amino acids		
	(B) TYPE: amino acid		
30	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
	(ii) MOLECULE TYPE: peptide		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:		
35	Ala Ile Gln Ala Pro Phe Leu Trp Val Leu Phe Leu Leu Ala Ala Leu		
	1	5	10
	15		
	Glu Asn Ile Phe Val Leu Ser Val Phe Cys Leu His Lys Thr Asn Cys		
	20	25	30
	Thr Val Ala Glu Ile Tyr Leu Gly Asn Ile Ala Ser Ala Asp Leu Ile		
	35	40	45
40	Ile Ala Cys Gly Leu Pro Phe Trp Ala Ile Thr Ile Ala Asn Asn Phe		
	50	55	60
	Asp Trp Leu Phe Gly Glu Val Leu Cys Arg Val Val Asn Leu Tyr Met		
	65	70	75
	80		
45	Asn Leu Tyr Ser Ser Ile Cys Phe Leu Val Ser Ile Asp Arg Tyr Leu		
	85	90	95
	Ala Leu Val Lys Thr Met Ser Asn Leu Arg Trp Ala Lys Leu Tyr Ser		
	100	105	110

- 101 -

	Leu Val Ile Trp Ser Cys Thr Leu Leu Leu Ser Ser Pro Met Leu Val
	115 120 125
	Phe Arg Thr Met Tyr Arg Glu Glu Gly His Asn Val Thr Cys Val Ile
	130 135 140
5	Val Tyr Pro Ser Arg Ser Trp Glu Val Phe Leu Leu Asn Leu Val Gly
	145 150 155 160
	Phe Leu Leu Pro Leu Ser Ile Ile Thr Phe Cys Thr Val Arg Ile Met
	165 170 175
10	Val Leu Arg Asn Asn Glu Met Lys Lys Phe Lys Glu Val Gln Thr Glu
	180 185 190
	Lys Lys Ala Thr Val Leu Val Ile Ala Val Leu Gly Leu Phe Val Leu
	195 200 205
	Cys Trp Phe Pro Phe Gln Ile Ser Thr Phe Leu Asp Thr Leu Leu Arg
	210 215 220
15	Leu Gly Val Leu Ser Gly Cys Trp Asn Glu Arg Ala Val Asp Ile Val
	225 230 235 240
	Arg Gln Ile Ser Ser Tyr Val Ala Tyr Ser Asn Ser Cys Leu Asn Pro
	245 250 255
20	Leu Val Tyr Val Ile Val Gly Lys Arg Phe Arg Lys Lys Ser Arg Glu
	260 265 270
	Val Tyr Gln Ala Ile Cys Arg Lys Gly Gly Cys Met Gly Glu Ser Val
	275 280 285
	Leu Asn Ser Met Gly Thr Leu Arg Thr Ser Ile Ser Val Asp Arg Gln
	290 295 300
25	Ile His Lys Leu Gln Asp Trp Ala Gly Asn Lys Gln
	305 310 315
	(2) INFORMATION FOR SEQ ID NO:47:
	(i) SEQUENCE CHARACTERISTICS:
	(A) LENGTH: 347 amino acids
30	(B) TYPE: amino acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear
	(ii) MOLECULE TYPE: peptide
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:
35	Ile Leu Leu Val Val Ile Ile Cys Gly Leu Gly Ile Val Gl; Asn Ile
	1 5 10 15
	Met Val Val Leu Val Val Met Arg Thr Thr Pro Thr Asn Cys Tyr Leu
	20 25 30
40	Val Ser Ile Ala Val Ala Asp Leu Met Val Leu Val Ala Ala Gly Leu
	35 40 45
	Pro Asn Ile Thr Asp Ser Ile Tyr Gly Ser Trp Val Tyr Gly Tyr Val
	50 55 60
	Gly Cys Leu Cys Ile Thr Tyr Leu Gln Tyr Leu Gly Ile Asn Ala Ser
	65 70 75 80
45	Ser Cys Ser Ile Thr Ala Phe Thr Ile Glu Arg Tyr Ile Ala Ile Cys
	85 90 95
	His Pro Ile Lys Ala Gln Phe Leu Cys Thr Phe Ser Arg Ala Lys Lys

- 102 -

	100	105	110	
	Ile Ile Ile Phe Val Trp Ala Phe Thr Ser Ile Tyr Leu Phe Leu Leu			
	115	120	125	
5	Asp Ile Asn Ile Ser Thr Tyr Lys Asn Ala Val Val Val Ser Cys Gly			
	130	135	140	
	Tyr Lys Ile Ser Arg Asn Tyr Tyr Ser Pro Ile Tyr Leu Met Asp Phe			
	145	150	155	160
	Gly Val Phe Tyr Val Val Pro Leu Ile Ala Thr Val Leu Tyr Gly Phe			
	165	170	175	
10	Ile Ala Arg Ile Leu Phe Leu Asn Pro Ile Pro Ser Asp Pro Lys Glu			
	180	185	190	
	Asn Ser Lys Met Trp Lys Asn Asp Ser Ile His Gln Asn Lys Asn Leu			
	195	200	205	
15	Asn Leu Asn Ala Ser Ser Arg Lys Gln Val Thr Ile Asn Leu Ala Val			
	210	215	220	
	Val Val Ile Leu Phe Ala Leu Leu Trp Asn Thr Tyr Arg Thr Leu Val			
	225	230	235	240
	Val Val Asn Ser Phe Leu Ser Ser Pro Phe Gln Glu Asn Trp Lys Leu			
	245	250	255	
20	Leu Lys Cys Arg Ile Cys Ile Tyr Leu Asn Ser Ala Ile Asn Pro Val			
	260	265	270	
	Ile Tyr Asn Ile Met Ser Gln Lys Arg Phe Ala Ala Phe Arg Lys Leu			
	275	280	285	
25	Cys Asn Cys Lys Gln Lys Pro Thr Glu Lys Ala Ala Asn Tyr Ser Val			
	290	295	300	
	Ala Leu Asn Tyr Ser Val Ile Lys Glu Ser Asp Arg Phe Ser Thr Glu			
	305	310	315	320
	Leu Glu Asp Ile Thr Val Thr Asp Thr Tyr Val Ser Thr Thr Lys Val			
	325	330	335	
30	Ser Phe Asp Asp Thr Cys Ile Ala Ser Glu Asn			
	340	345		
(2) INFORMATION FOR SEQ ID NO:48:				
	(i) SEQUENCE CHARACTERISTICS:			
35	(A) LENGTH: 341 amino acids			
	(B) TYPE: amino acid			
	(C) STRANDEDNESS: single			
	(D) TOPOLOGY: linear			
	(ii) MOLECULE TYPE: peptide			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:			
40	Leu Ala Leu Trp Ala Thr Ala Tyr Leu Ala Leu Val Leu Va. Ala Val			
	1	5	10	15
	Thr Gly Asn Ala Ile Val Ile Trp Ile Ii Leu Ala His Arg Arg Met			
	20	25	30	
45	Arg Thr Val Thr Asn Tyr Phe Ile Val Asn Ile Ala Leu Ala Asp Leu			
	35	40	45	
	Leu Asn Ala Ala Phe Asn Phe Val Tyr Ala Ser His Asn Ile Trp Tyr			

- 103 -

	50	55	60													
	Phe	Gly	Arg	Ala	Phe	Cys	Tyr	Phe	Gln	Asn	Leu	Phe	Pro	Ile	Thr	Ala
	65					70			75							80
5	Met	Phe	Val	Ser	Ile	Tyr	Ser	Met	Thr	Ala	Ile	Ala	Ala	Asp	Arg	Tyr
					85				90						95	
	Met	Ala	Ile	Val	His	Pro	Phe	Gln	Pro	Arg	Leu	Ser	Ala	Pro	Ser	Thr
					100				105						110	
	Lys	Ala	Val	Ile	Ala	Gly	Ile	Trp	Leu	Val	Ala	Ile	Lys	Leu	Ala	Phe
					115				120						125	
10	Pro	Gln	Cys	Phe	Tyr	Ser	Thr	Val	Thr	Met	Gln	Gly	Ala	Thr	Lys	Cys
					130			135							140	
	Val	Val	Ala	Trp	Pro	Glu	Asp	Ser	Gly	Gly	Lys	Thr	Leu	Leu	Leu	Tyr
					145			150			155				160	
15	His	Leu	Val	Val	Ile	Ala	Leu	Ile	Tyr	Phe	Leu	Pro	Ile	Ala	Leu	Ala
					165				170						175	
	Tyr	Ser	Val	Ile	Gly	Leu	Thr	Leu	Trp	Arg	Arg	Ala	Val	Pro	Gly	His
					180			185							190	
	Gln	Ala	His	Gly	Ala	Asn	Leu	Arg	His	Leu	Gln	Ala	Lys	Lys	Phe	
					195			200							205	
20	Val	Lys	Thr	Met	Val	Leu	Val	Val	Val	Thr	Phe	Ala	Ile	Cys	Trp	Leu
					210			215							220	
	Pro	Tyr	His	Leu	Tyr	Phe	Ile	Leu	Gly	Ser	Phe	Gln	Glu	Asp	Ile	Tyr
					225			230							240	
25	Cys	His	Lys	Phe	Ile	Gln	Gln	Val	Tyr	Leu	Ala	Leu	Phe	Trp	Leu	Ala
					245			250							255	
	Met	Ser	Ser	Thr	Met	Tyr	Asn	Pro	Ile	Ile	Tyr	Cys	Cys	Leu	Asn	His
					260			265							270	
	Arg	Phe	Arg	Ser	Gly	Phe	Arg	Leu	Ala	Phe	Arg	Cys	Cys	Pro	Trp	Val
					275			280							285	
30	Thr	Pro	Thr	Lys	Glu	Asp	Lys	Leu	Glu	Leu	Thr	Pro	Thr	Thr	Ser	Leu
					290			295							300	
	Ser	Thr	Arg	Val	Asn	Arg	Cys	His	Thr	Lys	Glu	Thr	Leu	Phe	Met	Ala
					305			310							320	
35	Gly	Asp	Thr	Ala	Pro	Ser	Glu	Ala	Thr	Ser	Gly	Glu	Ala	Gly	Arg	Pro
					325					330					335	
	Gln	Asp	Gly	Ser	Gly											
					340											

## (2) INFORMATION FOR SEQ ID NO:49:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 340 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## 45 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Ile	Val	Leu	Trp	Ala	Ala	Ala	Tyr	Thr	Val	Ile	Val	Val	Arg	Ser	Val
1										5					10

- 104 -

	Val	Gly	Asn	Val	Val	Val	Ile	Trp	Ile	Ile	Leu	Ala	His	Lys	Arg	Met	
				20					25				30				
	Arg	Thr	Val	Thr	Asn	Tyr	Phe	Leu	Val	Asn	Ile	Ala	Phe	Ala	Phe	Ala	
				35					40				45				
5	Leu	Asn	Thr	Trp	Asn	Phe	Thr	Tyr	Ala	Val	His	Asn	Val	Trp	Tyr	Tyr	
				50				55				60					
	Gly	Leu	Phe	Tyr	Cys	Lys	Phe	His	Asn	Phe	Phe	Pro	Ile	Ala	Ala	Leu	
				65				70			75				80		
10	Phe	Ala	Ser	Ile	Tyr	Ser	Met	Thr	Ala	Val	Ala	Phe	Asp	Arg	Tyr	Leu	
				85				90				95					
	Ile	Ile	His	Pro	Leu	Gln	Pro	Arg	Leu	Ser	Ala	Thr	Ala	Thr	Lys	Val	
				100				105				110					
	Val	Ile	Phe	Val	Ile	Trp	Val	Ile	Ala	Leu	Leu	Leu	Ala	Ser	Pro	Gln	
				115				120				125					
15	Gly	Tyr	Tyr	Ser	Thr	Thr	Glu	Leu	Ser	Arg	Val	Val	Cys	Met	Ile	Glu	
				130				135				140					
	Trp	Pro	Glu	His	Pro	Asn	Arg	Thr	Tyr	Glu	Lys	Ala	Tyr	Hi-	Ile	Cys	
				145				150			155			160			
20	Val	Thr	Val	Leu	Ile	Tyr	Phe	Leu	Pro	Leu	Leu	Val	Ile	Gly	Tyr	Ala	
				165				170				175					
	Tyr	Thr	Val	Val	Gly	Ile	Thr	Leu	Trp	Ala	Ser	Glu	Ile	Pro	Gly	Asp	
				180				185				190					
	Ser	Ser	Asp	Arg	Tyr	His	Glu	Gln	Val	Ser	Ala	Lys	Arg	Lys	Val	Val	
				195				200				205					
25	Lys	Met	Ile	Cys	Val	Val	Val	Cys	Thr	Phe	Ala	Ile	Cys	Trp	Leu	Pro	
				210				215				220					
	Phe	His	Val	Phe	Phe	Leu	Leu	Pro	Tyr	Ile	Asn	Pro	Asp	Leu	Tyr	Leu	
				225				230			235			240			
30	Lys	Lys	Phe	Ile	Gln	Gln	Val	Tyr	Ile	Ala	Ser	Met	Trp	Leu	Ala	Met	
				245				250				255					
	Ser	Ser	Thr	Met	Tyr	Asn	Pro	Ile	Ile	Tyr	Cys	Cys	Leu	Asn	Asp	Arg	
				260				265				270					
	Phe	Arg	Leu	Gly	Phe	Lys	His	Ala	Phe	Arg	Cys	Cys	Pro	Phe	Ile	Ser	
				275				280				285					
35	Ala	Gly	Asp	Tyr	Gl	Leu	Gly	Leu	Glu	Met	Ile	Lys	Ser	Thr	Arg	Tyr	Leu
				290				295				300					
	Gln	Thr	Leu	Ser	Ser	Val	Tyr	Lys	Val	Ser	Arg	Leu	Glu	Thr	Thr	Ile	
				305				310			315			320			
40	Ser	Thr	Val	Val	Gly	Ala	His	Glu	Glu	Pro	Glu	Glu	Gly	Pro	Lys		
				325				330				335					
	Ala	Thr	Pro	Ser													
				340													

## (2) INFORMATION FOR SEQ ID NO:50:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 336 amino acids
- (B) TYPE: amino acid

45

- 105 -

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

5	Ile Ala Leu Trp Ser Leu Ala Tyr Gly Leu Val Val Ala Val Ala Val 1                       5                       10                       15
	Phe Gly Asn Leu Ile Val Ile Trp Ile Ile Leu Ala His Lys Arg Met 20                      25                       30
10	Arg Thr Val Thr Asn Tyr Phe Leu Val Asn Leu Ala Phe Ser Asp Ala 35                      40                       45
	Ser Val Ala Ala Phe Asn Thr Leu Ile Asn Phe Ile Tyr Gly Leu His 50                      55                       60
	Ser Glu Trp Tyr Phe Gly Ala Asn Tyr Cys Arg Phe Gln Asn Phe Phe 65                      70                       75                       80
15	Pro Ile Thr Ala Val Phe Ala Ser Ile Tyr Ser Met Ala Ile Ala Val 85                      90                       95
	Asp Arg Tyr Met Ala Ile Ile Asp Pro Leu Lys Pro Arg Leu Ser Ala 100                    105                       110
20	Thr Ala Thr Lys Ile Val Ile Gly Ser Ile Trp Ile Leu Ala Phe Leu 115                    120                       125
	Leu Ala Phe Pro Gln Cys Leu Tyr Ser Lys Ile Leu Gly Arg Thr Leu 130                    135                       140
	Cys Tyr Val Trp Pro Glu Gly Pro Lys Gln His Phe Thr Tyr His Ile 145                    150                       155                       160
25	Ile Val Ile Ile Leu Val Tyr Cys Phe Pro Leu Leu Ile Leu Thr Tyr 165                    170                       175
	Thr Ile Val Gly Ile Thr Leu Trp Gly Gly Glu Ile Pro Gly Asp Thr 180                    185                       190
30	Cys Asp Lys Tyr His Glu Gln Leu Lys Ala Lys Arg Lys Val Val Met 195                    200                       205
	Asn Ile Val Val Val Thr Phe Ala Ile Cys Trp Leu Pro Tyr His Val 210                    215                       220
	Tyr Phe Ile Leu Thr Ala Ile Tyr Gln Gln Leu Asn Arg Trp Lys Tyr 225                    230                       235                       240
35	Ile Gln Gln Val Tyr Leu Ala Ser Phe Trp Leu Ala Met Ser Ser Thr 245                    250                       255
	Met Tyr Asn Pro Ile Ile Tyr Cys Cys Leu Asn Lys Arg Phe Arg Ala 260                    265                       270
40	Gly Phe Lys Arg Ala Phe Arg Trp Cys Pro Phe Ile Gln Val Ser Ser 275                    280                       285
	Tyr Asp Glu Leu Glu Leu Lys Thr Thr Arg Phe His Pro Thr Arg Gln 290                    295                       300
	Ser Ser Leu Tyr Thr Val Ser Phe Met Ser Val Thr Val Leu Phe Asp 305                    310                       315                       320
45	Pro Asn Asp Gly Asp Pro Thr Lys Ser Ser Arg Lys Lys Arg Ala Val 325                    330                       335

- 106 -

## (2) INFORMATION FOR SEQ ID NO:51:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 325 amino acids

(B) TYPE: amino acid

5 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

	Met Ile Pro Thr Leu Tyr Ser Ile Ile Phe Val Val Gly Ile Phe Gly	
10	1 5 10 15	
	Asn Ser Leu Val Val Ile Val Ile Tyr Phe Tyr Met Lys Leu Lys Thr	
	20 25 30	
	Tyr Ala Ser Val Phe Leu Leu Asn Leu Ala Leu Asp Leu Cys Phe	
15	35 40 45	
	Leu Leu Thr Leu Pro Leu Trp Ala Val Tyr Thr Leu Tyr Arg Trp Pro	
	50 55 60	
	Phe Gly Asn Tyr Leu Cys Lys Ile Ala Ser Ala Ser Val Ser Phe Asn	
	65 70 75 80	
20	Leu Tyr Ala Ser Val Phe Leu Leu Thr Cys Leu Ser Ile Asp Arg Tyr	
	85 90 95	
	Leu Ala Ile Val His Pro Met Lys Ser Arg Leu Arg Arg Leu Val Ala	
	100 105 110	
	Lys Val Thr Cys Ile Ile Trp Leu Leu Ala Gly Ile Ala Ser Leu	
	115 120 125	
25	Pro Thr Ile Ile His Arg Asn Phe Phe Ile Glu Asn Thr Asn Ile Thr	
	130 135 140	
	Val Cys Ala Phe His Tyr Glu Ser Gln Asn Ser Thr Leu Pro Val Gly	
	145 150 155 160	
30	Leu Gly Leu Thr Lys Asn Ile Leu Gly Phe Leu Phe Pro Phe Leu Ile	
	165 170 175	
	Ile Leu Thr Ser Tyr Thr Leu Ile Trp Lys Thr Leu Lys Lys Ala Tyr	
	180 185 190	
	Glu Ile Gln Lys Asn Lys Pro Arg Lys Asp Asp Ile Phe Lys Ile Ile	
	195 200 205	
35	Ile Ala Ile Val Leu Phe Phe Phe Ser Trp Val Pro His Asn Ile	
	210 215 220	
	Phe Thr Phe Met Val Leu Ile Gln Leu Gly Leu Ile Arg Asp Cys Lys	
	225 230 235 240	
40	Ile Glu Asp Ile Val Asp Thr Ala Met Pro Ile Thr Ile Cys Leu Ala	
	245 250 255	
	Tyr Phe Gln Gln Asn Leu Asn Pro Leu Phe Tyr Gly Phe Leu Gly Lys	
	260 265 270	
	Lys Phe Lys Lys Tyr Phe Leu His Ala Leu Leu Lys Tyr Ile Pro Pro	
	275 280 285	
45	Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr Leu Ser	
	290 295 300	

- 107 -

Tyr Arg Pro Ser Glu Gln Gly Asn Ser Ser Thr Lys Lys Pro Ala Pro  
 305                   310                   315                   320

Cys Ile Glu Val Glu  
 325

5 (2) INFORMATION FOR SEQ ID NO:52:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 282 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:  
 Ile Val His Trp Val Ile Met Ser Ile Ser Pro Val Gly Phe Val Glu  
 1                   5                   10                   15

15 Asn Gly Ile Leu Leu Trp Phe Leu Cys Phe Phe Thr Val Tyr Thr His  
 20                   25                   30

Leu Ser Ile Ala Asp Ile Ser Leu Leu Phe Cys Ile Phe Ile Leu Ser  
 35                   40                   45

20 Ile Asp Tyr Ala Leu Asp Tyr Glu Leu Ser Ser Gly His Tyr Tyr Thr  
 50                   55                   60

Ile Val Thr Leu Ser Val Thr Phe Leu Phe Gly Tyr Asn Thr Gly Leu  
 65                   70                   75                   80

Tyr Leu Leu Thr Ala Ile Ser Val Glu Arg Cys Leu Ser Val Leu Tyr  
 85                   90                   95

25 Pro Ile Trp Tyr Arg Cys His Arg Pro Lys Tyr Gln Ser Ala Leu Val  
 100               105               110

Cys Ala Leu Leu Trp Ala Leu Ser Cys Leu Val Thr Thr Me Tyr Val  
 115               120               125

30 Met Cys Ile Asp Arg Phe Glu Glu Ser His Ser Arg Asn Asp Cys Arg  
 130               135               140

Ala Val Ile Ile Phe Ile Ala Ile Leu Ser Phe Leu Val Phe Thr Pro  
 145               150               155               160

Ser Val Ser Ser Thr Ile Leu Val Val Lys Ile Arg Lys Asn Thr Trp  
 165               170               175

35 Ala Ser His Ser Ser Lys Leu Tyr Ile Val Ile Met Val Thr Ile Ile  
 180               185               190

Ile Phe Leu Ile Phe Ala Met Pro Met Arg Leu Leu Tyr Leu Leu Tyr  
 195               200               205

40 Tyr Glu Tyr Trp Ser Thr Phe Gly Asn Leu His His Ile Ser Leu Leu  
 210               215               220

Phe Ser Thr Ile Asn Ser Ser Ala Asn Pro Phe Ile Tyr Phe Phe Val  
 225               230               235               240

---

Gly Ser Ser Lys Lys Lys Arg Phe Lys Glu Ser Leu Lys Val Val Leu  
 245               250               255

45 Thr Arg Ala Phe Lys Asp Glu Met Gln Pro Arg Arg Gln Lys Asp Asn  
 260               265               270

Cys Asn Thr Val Thr Val Glu Thr Val Val

- 108 -

275

280

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 332 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:  
Tyr Asp Phe Leu Arg Val Leu Ile Trp Leu Ile Asn Ile Leu Ala Ile  
1 5 10 15

Met Gly Asn Val Met Thr Leu Phe Val Leu Leu Thr Ser Arg Tyr Lys  
20 25 30

15 Leu Thr Val Pro Arg Phe Ile Met Asn Leu Ser Phe Ala Asp Phe Cys  
35 40 45

Met Leu Tyr Leu Leu Leu Ile Ala Ser Val Asp Ser Gln Thr Lys Gly  
50 55 60

Gln Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Ser Gly Cys Ser  
65 70 75 80

20           Thr Ala Gly Phe Phe Thr Val Leu Ala Ser Glu Leu Ser Val Tyr Thr  
              85                   90                   95

Leu Thr Val Ile Thr Leu Glu Arg Trp His Thr Ile Thr Tyr Ala Ile  
100 105 110

25 His Ile Asp Gln Lys Leu Arg Leu Arg His Ala Ile Leu Ile Met Leu  
115 120 125

Gly Gly Trp Leu Phe Ser Ser Leu Ile Ala Met Leu Pro Leu Val Cys  
130 135 140

Val Ser Asn Tyr Met Lys Val Ser Ile Cys Leu Pro Met Val Glu Thr  
145 150 155 160

30 Thr Leu Ser Gln Val Tyr Ile Leu Thr Ile Leu Ile Leu Asn Val Val  
165 170 175

Ala Phe Leu Ile Ile Cys Ala Cys Tyr Ile Lys Ile Tyr Phe Ala Val  
180 185 191

35 Arg Asn Pro Glu Ile Met Ala Thr Asn Lys Asp Thr Lys Ile Ala Leu  
           195                   200                   205

Aia file Leu Ile Phe Thr Asp Phe Thr Cys Met Pro Ile Ser Phe Phe  
210 215 220

Ala Ile Ser Ala Ala Phe Lys Val Pro Leu Ile Val Thr Asn Ser Lys  
225 230 235 240

40 Val Leu Leu Val Leu Phe Tyr Pro Ile Asn Ser Cys Ala Asn Pro Phe  
245 250 255

Leu Tyr Ala Ile Phe Thr Lys Thr Phe Gln Arg Asp Phe Phe Ile Leu  
260 265 270

Phe Ser Ala Tyr Thr Ser Asn Cys Lys Lys Gly Phe Thr Gly Ser Asn  
290 295 300

- 109 -

Lys Pro Ser Gln Ser Thr Leu Lys Leu Ser Thr Leu His Cys Gln Gly  
 305                   310                   315                   320

Thr Ala Leu Leu Asp Lys Arg Arg Tyr Thr Glu Cys  
325 330

5 (2) INFORMATION FOR SEQ ID NO:54

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 336 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: sin

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54.

Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser Leu Leu Ala Leu  
1 5 10 15

15 Leu Gly Asn Val Phe Val Leu Leu Ile Leu Leu Thr Ser His Tyr Lys  
20 25 30

Leu Asn Val Pro Arg Phe Ile Met Asn Ile Ala Phe Ala Asp Phe Cys  
35 40 45

20 Met Met Tyr Leu Leu Leu Ile Ala Ser Val Asp Leu Tyr Thr His Ser  
50 55 60

Thr Ala Gly Phe Phe Thr Val Phe Ala Ser Glu Leu Ser Val Tyr Thr  
85 90 95

Leu Thr Val Ile Thr Leu Glu Arg Trp Tyr Ala Ile Thr Phe Ala Met  
100 105 110

Arg Leu Asp Arg Lys Ile Arg Leu Arg His Ala Cys Ala Ile Met Val  
115 120 125

Gly Gly Trp Val Cys Cys Phe Leu Leu Ala Leu Leu Pro Leu Val Gly

Ile Ser Ser Tyr Ala Lys Val Ser Ile Cys Leu Pro Met Thr Glu Thr

Pro Leu Ala Leu Ala Tyr Ile Val Phe Val Leu Thr Leu Asn Ile Val

35 Ala Phe Val Ile Val Cys Cys Cys Tyr Val Lys Ile Tyr Ile Thr Val

Arg Asn Pro Gln Tyr Asn Pro Gly Asp Lys Asp Thr Lys Ile Ala Lys

Arg Met Ala Val Leu Ile Phe Thr Asp Phe Ile Cys Met Ala Pro Ile

Ser Phe Tyr Ala Leu Ser Ala Ile Leu Asn Lys Pro Leu Ile Thr Val

Ser Asn Ser Lys Ile Leu Leu Val Leu Phe Tyr Pro Leu Asn Ser Cys

Ala Asn Pro Phe Leu Tyr Ala Ile Phe Thr Lys Ala Phe Gln Arg Asp

260 265 270

- 210 -

Val Phe Ile Leu Leu Ser Lys Phe Gly Ile Cys Lys Arg Gln Ala Gln  
275 280 285

Ala Tyr Arg Gly Gln Arg Val Pro Pro Lys Asn Ser Thr Asp Ile Gln  
290 295 300

5 Val Gln Lys Val Thr His Asp Met Arg Gln Gly Ala Leu Asn Met Glu  
305 310 315 320

Asp Val Val Glu Leu Ile Glu Asn Ser His Leu Thr Pro Lys Lys Gln  
325 330 335

(2) INFORMATION FOR SEQ ID NO:55:

10 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 327 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Tyr Asn Ile Leu Arg Val Leu Ile Trp Phe Ile Ser Ile Leu Ala Ile  
1 5 10 15

20 Thr Gly Asn Ile Ile Val Leu Val Ile Leu Thr Thr Ser Gln Tyr Lys  
                   20                         25                         30

Leu Thr Val Pro Arg Phe Leu Met Asn Ile Ala Phe Ala Asp Leu Cys  
35 40 45

Ile Gly Ile Tyr Leu Leu Leu Ile Ala Ser Val Asp Ile His Thr Lys  
50 55 60

25 Ser Gln Tyr His Asn Tyr Ala Ile Asp Trp Gln Arg Gly Ala Gly Cys  
65 70 75 80

Asp Ala Ala Gly Phe Phe Thr Val Phe Ala Ser Glu Leu Ser Val Tyr  
85 90 95

30 Thr Leu Thr Ala Ile Thr Leu Glu Arg Trp His Thr Ile Thr His Ile  
100 105 110

Met Gln Ile Asp Cys Lys Val Gln Leu Arg His Ala Ala Ser Val Met  
115 . 120 125

Val Met Gly Trp Ile Phe Ala Phe Ala Ala Ala Leu Phe Pro Ile Phe  
130 135 140

Gly Ile Ser Ser Tyr Met Lys Val Ser Ile Cys Leu Pro Leu Ile Asp  
145 150 155 160

Ser Pro Leu Ser Gln Leu Tyr Val Met Ser Leu Leu Val Leu Asn Val  
165 170 175

Leu Ala Phe Val Val Ile Cys Gly Cys Tyr Thr His Ile Tyr Leu Thr  
180 185 190

Val Arg Asn Pro Asn Ile Val Ser Ser Ser Ser Asp Thr Arg Ile Ala  
195 200 205

Lys Arg Met Leu Ile Phe Thr Asp Phe Leu Leu Pro Ile Ser Phe Phe  
210 . 215 . 220

45 Ala Ile Ser Ala Ser Leu Lys Val Pro Leu Ile Thr Val Ser Lys Ala  
225 230 235 240

Lys Ile Leu Leu Val Leu Phe His Pro Ile Asn Ser Cys Ala Asn Pro

- III -

	245	250	255
	Phe Leu Tyr Ala Ile Phe Thr Lys Asn Phe Arg Arg Asp Phe Phe Ile		
	260	265	270
5	Leu Leu Ser Lys Cys Gly Cys Tyr Glu Met Gln Ala Gln Ile Tyr Arg		
	275	280	285
	Thr Glu Thr Ser Ser Thr Val His Asn Thr His Pro Arg Asn Gly His		
	290	295	300
	Cys Ser Ser Ala Pro Arg Val Thr Ser Gly Ser Ser Arg Tyr Ile Leu		
	305	310	315
10	Val Pro Leu Ser Leu Gln Asn		
	325		
	(2) INFORMATION FOR SEQ ID NO:56:		
	(i) SEQUENCE CHARACTERISTICS:		
15	(A) LENGTH: 309 amino acids		
	(B) TYPE: amino acid		
	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
	(ii) MOLECULE TYPE: peptide		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:		
20	Ser Met Leu Ala Ala Tyr Met Phe Leu Leu Ile Val Leu Gly Phe Pro		
	1	5	10
	Ile Asn Phe Leu Thr Leu Tyr Val Thr Val Gln His Lys Lys Leu Arg		
	20	25	30
25	Thr Pro Ile Asn Tyr Ile Leu Leu Asn Leu Ala Val Ala Asp Leu Phe		
	35	40	45
	Met Val Leu Gly Gly Phe Thr Ser Thr Leu Tyr Thr Ser Leu His Gly		
	50	55	60
	Tyr Phe Val Phe Gly Pro Thr Gly Cys Asn Leu Glu Gly Phe Phe Ala		
	65	70	75
30	80		
	Thr Leu Gly Gly Clu Ile Ala Leu Trp Ser Leu Trp Leu Ala Ile Glu		
	85	90	95
	Arg Tyr Val Val Val Cys Lys Pro Met Ser Asn Phe Arg Phe Gly Glu		
	100	105	110
35	Asn His Ala Ile Met Gly Val Ala Phe Thr Trp Val Met Ala Leu Ala		
	115	120	125
	Cys Ala Ala Pro Pro Ile Ala Gly Trp Ser Arg Tyr Ile Pro Glu Gly		
	130	135	140
	Leu Gln Cys Ser Cys Gly Ile Asp Tyr Tyr Thr Leu Lys Pro Glu Val		
	145	150	155
	160		
40	Asn Asn Glu Ser Phe Val Ile Tyr Met Phe Val Val His Phe Thr Ile		
	165	170	175
	Pro Leu Ile Ile Phe Phe Cys Tyr Gly Gln Leu Val Phe Thr Val Lys		
	180	185	190
45	Glu Ala Ala Ala Gln Gln Glu Ser Ala Thr Thr Gln Lys Ala Glu		
	195	200	205
	Lys Glu Val Thr Arg Met Val Ile Ile Met Val Ile Ala Phe Leu Ile		
	210	215	220

- 112 -

Cys Trp Val Pro Tyr Ala Ser Val Ala Phe Tyr Ile Phe Thr His Gln  
 225                    230                    235                    240

Gly Ser Asn Phe Gly Pro Ile Phe Met Arg Ile Pro Ala Phe Phe Ala  
 245                    250                    255

5       Lys Ser Ala Ala Ile Tyr Asn Pro Val Ile Tyr Ile Ile Phe Asn Lys  
 260                    265                    270

Gln Phe Arg Asn Cys Met Leu Gln Leu Ile Cys Cys Gly Lys Asn Pro  
 275                    280                    285

10      Leu Gly Asp Asp Glu Ala Ser Ala Thr Val Ser Lys Arg Glu Thr Ser  
 290                    295                    300

Gln Val Ala Pro Ala  
 305

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

15      (A) LENGTH: 297 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

20      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:  
 Met Ile Phe Val Val Ile Ala Ser Val Phe Thr Asn Gly Leu Val Leu  
 1                    5                    10                    15

Ala Ala Thr Met Lys Phe Lys Lys Leu Pro His Pro Ile Asn Trp Ile  
 20                    25                    30

25      Leu Val Asn Leu Ala Val Ala Asp Ile Ala Gly Thr Val Ile Ala Ser  
 35                    40                    45

Thr Ile Ser Val Val Asn Gln Val Tyr Gly Tyr Phe Val Leu Gly His  
 50                    55                    60

30      Pro Met Cys Val Leu Glu Gly Tyr Thr Val Ser Leu Cys Gly Ile Thr  
 65                    70                    75                    80

Gly Leu Trp Ser Leu Ala Ile Ile Ser Trp Glu Arg Trp Met Val Val  
 85                    90                    95

Cys Lys Pro Phe Gly Asn Val Arg Phe Asp Ala Lys Ile Ala Ile Val  
 100                    105                    110

35      Gly Ile Ala Phe Ser Trp Ile Trp Ala Ala Val Trp Thr Ala Pro Pro  
 115                    120                    125

Ile Phe Gly Trp Ser Arg Tyr Trp Pro His Gly Leu Lys Thr Ser Cys  
 130                    135                    140

40      Gly Pro Asp Val Phe Ser Gly Ser Ser Tyr Pro Gly Val Gln Ser Leu  
 145                    150                    155                    160

Leu Cys Ile Thr Pro Leu Ser Ile Ile Val Leu Cys Tyr Leu Gln Val  
 165                    170                    175

Trp Thr Ala Ile Arg Ala Val Ala Lys Gln Gln Lys Glu Ser Glu Ser  
 180                    185                    190

45      Thr Gln Lys Ala Glu Lys Glu Val Thr Arg Met Trp Val Met Val Leu  
 195                    200                    205

Ala Phe Cys Phe Cys Trp Gly Pro Tyr Ala Phe Phe Ala Cys Phe Ala

- 113 -

	210	215	220
	Ala Ala Asn Pro Gly Tyr Pro Phe His Pro Leu Met Ala Ala Leu Pro		
	225	230	235
	240		
	Ala Phe Phe Ala Lys Ser Ala Thr Ile Tyr Asn Pro Val Ile Tyr Val		
5	245	250	255
	Phe Met Asn Arg Gln Phe Arg Asn Cys Ile Leu Gln Leu Phe Gly Lys		
	260	265	270
	Lys Val Asp Asp Gly Ser Glu Leu Ser Ser Ala Ser Lys Thr Glu Val		
	275	280	285
10	Ser Ser Val Ser Ser Val Ser Pro Ala		
	290	295	
	(2) INFORMATION FOR SEQ ID NO:58:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 297 amino acids		
15	(B) TYPE: amino acid		
	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
	(ii) MOLECULE TYPE: peptide		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:		
20	Arg Cys Phe Val Val Thr Ala Ser Val Phe Thr Asn Gly Leu Val Leu		
	1	5	10
	15		
	Ala Ala Thr Met Lys Phe Lys Lys Leu Arg His Pro Leu Asn Trp Ile		
	20	25	30
25	Leu Val Asn Ile Ala Val Ala Asp Ile Ala Gly Thr Val Ile Ala Ser		
	35	40	45
	Thr Ile Ser Ile Val Asn Gln Val Ser Gly Tyr Phe Val Leu Gly His		
	50	55	60
	Pro Met Cys Val Leu Glu Gly Tyr Thr Val Ser Leu Cys Gly Ile Thr		
	65	70	75
	80		
30	Gly Leu Trp Ser Leu Ala Ile Ile Ser Trp Glu Arg Trp Leu Trp Cys		
	85	90	95
	Lys Pro Phe Gly Asn Val Arg Phe Asp Ala Lys Ile Ala Ile Val Gly		
	100	105	110
35	Ile Ala Phe Ser Trp Ile Trp Ser Ala Val Trp Thr Ala Pro Pro Ile		
	115	120	125
	Phe Gly Trp Ser Arg Tyr Trp Pro His Gly Leu Lys Thr Ser Cys Gly		
	130	135	140
	Pro Asp Val Phe Ser Gly Ser Ser Tyr Pro Gly Val Gln Ser Leu Val		
	145	150	155
	160		
40	Ile Met Val Thr Cys Cys Ile Ile Pro Ile Ala Ile Ile Leu Cys Tyr		
	165	170	175
	Leu Gln Val Trp Leu Ala Ile Arg Ala Val Ala Lys Gln Gln Lys Glu		
	180	185	190
45	Ser Glu Ser Thr Gln Lys Ala Glu Lys Glu Val Thr Arg Met Leu Phe		
	195	200	205
	Ala Tyr Cys Val Cys Trp Gly Pro Tyr Thr Phe Phe Ala Cys Phe Ala		
	210	215	220

- 114 -

Ala Ala Asn Pro Gly Tyr Ala Phe His Pro Leu Met Ala Ala Leu Pro  
 225 230 235 240  
 Ala Tyr Phe Ala Lys Ser Ala Thr Ile Tyr Asn Pro Val Ile Tyr Val  
 245 250 255  
 5 Phe Met Asn Arg Gln Phe Arg Asn Cys Ile Leu Gln Leu Phe Gly Lys  
 260 265 270  
 Lys Val Asp Asp Gly Ser Glu Leu Ser Ser Ala Ser Lys Thr Glu Val  
 275 280 285  
 10 Ser Ser Val Ser Ser Val Ser Pro Ala  
 290 295

(2) INFORMATION FOR SEQ ID NO:59:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 305 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Gln	Ala	Ala	Phe	Met	Gly	Thr	Val	Phe	Leu	Ile	Gly	Phe	Pro	Leu	Leu
1				5					10				15		

Val Ala Thr Leu Ala Tyr Lys Lys Leu Arg Gln Pro Asn Tyr Ile Leu  
 20 25 30

Val Asn Val Ser Phe Gly Gly Phe Leu Leu Cys Ile Phe Ser Val Phe  
 35 40 45

25 Pro Val Phe Val Ala Ser Cys Asn Gly Tyr Phe Val Phe Gly Arg His  
 50 55 60

Val Cys Ala Leu Glu Gly Phe Leu Gly Thr Val Ala Gly Leu Val Thr  
 65 70 75 80

30 Gly Trp Ser Leu Ala Phe Leu Ala Phe Glu Arg Tyr Ile Val Ile Cys  
 85 90 95

Lys Pro Phe Gly Asn Phe Arg Phe Ser Ser Lys His Ala Leu Thr Val  
 100 105 110

Val Ile Ala Thr Trp Thr Ile Gly Ile Gly Val Ser Ile Pro Pro Phe  
 115 120 125

35 Phe Gly Trp Ser Arg Phe Ile Pro Glu Gly Leu Gln Cys Ser Cys Gly  
 130 135 140

Pro Asp Lys Tyr Thr Val Gly Thr Lys Tyr Arg Ser Glu Ser Tyr Thr  
 145 150 155 160

40 Trp Phe Leu Phe Ile Phe Cys Phe Ile Val Pro Leu Ser Leu Ile Cys  
 165 170 175

Phe Ser Tyr Thr Gln Leu Leu Arg Ala Leu Lys Ala Val Ala Ala Gln  
 180 185 190

Gln Gln Glu Ser Ala Thr Thr Gln Lys Ala Glu Arg Glu Val Ser Arg  
 195 200 205

45 Met Val Val Val Met Val Gly Ser Phe Cys Val Cys Tyr Val Pro Tyr  
 210 215 220

Ala Ala Phe Ala Met Tyr Met Val Asn Asn Arg Asn His Gly Leu Asp

- 115 -

	225	230	235	240
	Leu Arg Leu Val Arg Ile Pro Ser Phe Phe Ser Lys Ser Ala Cys Ile			
	245	250		255
5	Tyr Asn Pro Ile Ile Tyr Cys Phe Met Asn Lys Gln Phe Gln Ala Cys			
	260	265		270
	Ile Met Met Val Cys Gly Lys Ala Met Met Glu Ser Asp Thr Cys Ser			
	275	280		285
	Ser Gln Lys Thr Glu Val Ser Thr Val Ser Ser Thr Gln Val Gly Pro			
	290	295		300
10	Asn			
	305			
	(2) INFORMATION FOR SEQ ID NO:60:			
	(i) SEQUENCE CHARACTERISTICS:			
15	(A) LENGTH: 293 amino acids			
	(B) TYPE: amino acid			
	(C) STRANDEDNESS: single			
	(D) TOPOLOGY: linear			
	(ii) MOLECULE TYPE: peptide			
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:			
	Leu Ile Tyr Gly Leu Phe Leu Ser Met Tyr Leu Val Thr Val Ile Gly			
	1	5	10	15
	Asn Ile Ser Ile Ile Val Ala Ile Ile Ser Asp Pro Cys Leu His Thr			
	20	25		30
25	Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Ile Cys Phe			
	35	40		45
	Ile Ser Thr Thr Val Pro Val Asn Thr Gln Thr Gln Asn Asn Val Ile			
	50	55		60
	Thr Tyr Ala Gly Cys Ile Thr Gln Ile Tyr Phe Phe Leu Leu Phe Val			
	65	70		80
30	Glu Leu Asp Asn Phe Leu Leu Thr Ile Met Ala Tyr Asp Arg Tyr Val			
	85	90		95
	Ala Ile Cys His Pro Met His Tyr Thr Val Ile Met Asn Tyr Lys Leu			
	100	105		110
35	Cys Gly Phe Leu Val Leu Val Ser Trp Ile Val Ser Val Leu His Ala			
	115	120		125
	Leu Phe Gln Ser Leu Ala Leu Pro Phe Cys Thr His Leu Glu Ile Pro			
	130	135		140
	His Tyr Phe Cys Glu Pro Asn Gln Val Ile Gln Leu Thr Cys Ser Asp			
	145	150		160
40	Ala Phe Leu Asn Asp Leu Val Ile Tyr Phe Thr Leu Val Leu Leu Ala			
	165	170		175
	Thr Val Pro Ile Ala Gly Ile Phe Tyr Ser Tyr Phe Ala Ile Ser Ser			
	180	185		19
45	Val His Gly Lys Tyr Lys Ala Phe Ser Thr Cys Ala Ser His Leu Ser			
	195	200		205
	Val Val Ser Leu Phe Tyr Cys Thr Gly Leu Gly Val Tyr Leu Ser Ser			
	210	215		220

- 116 -

	Ala Ala Asn Asn Ser Leu Ser Ala Thr Ala Ser Val Met Tyr Thr Val																																																																																																																																																									
225	230		235		240		Val Thr Pro Met Val Asn Pro Phe Ile Tyr Ser Leu Arg Asn Lys Asp	245	250		255	5	Val Lys Ser Val Leu Lys Lys Thr Leu Cys Glu Glu Val Ile Arg Ser		260		265		270		Pro Pro Ser Leu Leu His Phe Phe Leu Val Leu Cys His Leu Pro Cys		275		280		285	10	Phe Ile Phe Cys Tyr		290		(2) INFORMATION FOR SEQ ID NO:61:		(i) SEQUENCE CHARACTERISTICS:		(A) LENGTH: 284 amino acids		(B) TYPE: amino acid	15	(C) STRANDEDNESS: single		(D) TOPOLOGY: linear		(ii) MOLECULE TYPE: peptide		(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:	20	Leu Leu Phe Leu Leu Phe Leu Ile Met Tyr Leu Ala Thr Val Leu Gly		1	5		10		15		Asn Leu Leu Ile Ile Leu Ala Ile Gly Gly Asp Ser Arg Leu His Thr		20	25		30		Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe		35	40		45	25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser		50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly
	235		240		Val Thr Pro Met Val Asn Pro Phe Ile Tyr Ser Leu Arg Asn Lys Asp	245	250		255	5	Val Lys Ser Val Leu Lys Lys Thr Leu Cys Glu Glu Val Ile Arg Ser		260		265		270		Pro Pro Ser Leu Leu His Phe Phe Leu Val Leu Cys His Leu Pro Cys		275		280		285	10	Phe Ile Phe Cys Tyr		290		(2) INFORMATION FOR SEQ ID NO:61:		(i) SEQUENCE CHARACTERISTICS:		(A) LENGTH: 284 amino acids		(B) TYPE: amino acid	15	(C) STRANDEDNESS: single		(D) TOPOLOGY: linear		(ii) MOLECULE TYPE: peptide		(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:	20	Leu Leu Phe Leu Leu Phe Leu Ile Met Tyr Leu Ala Thr Val Leu Gly		1	5		10		15		Asn Leu Leu Ile Ile Leu Ala Ile Gly Gly Asp Ser Arg Leu His Thr		20	25		30		Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe		35	40		45	25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser		50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly		
	240																																																																																																																																																									
	Val Thr Pro Met Val Asn Pro Phe Ile Tyr Ser Leu Arg Asn Lys Asp																																																																																																																																																									
245	250		255	5	Val Lys Ser Val Leu Lys Lys Thr Leu Cys Glu Glu Val Ile Arg Ser		260		265		270		Pro Pro Ser Leu Leu His Phe Phe Leu Val Leu Cys His Leu Pro Cys		275		280		285	10	Phe Ile Phe Cys Tyr		290		(2) INFORMATION FOR SEQ ID NO:61:		(i) SEQUENCE CHARACTERISTICS:		(A) LENGTH: 284 amino acids		(B) TYPE: amino acid	15	(C) STRANDEDNESS: single		(D) TOPOLOGY: linear		(ii) MOLECULE TYPE: peptide		(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:	20	Leu Leu Phe Leu Leu Phe Leu Ile Met Tyr Leu Ala Thr Val Leu Gly		1	5		10		15		Asn Leu Leu Ile Ile Leu Ala Ile Gly Gly Asp Ser Arg Leu His Thr		20	25		30		Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe		35	40		45	25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser		50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly								
	255																																																																																																																																																									
5	Val Lys Ser Val Leu Lys Lys Thr Leu Cys Glu Glu Val Ile Arg Ser																																																																																																																																																									
	260		265		270		Pro Pro Ser Leu Leu His Phe Phe Leu Val Leu Cys His Leu Pro Cys		275		280		285	10	Phe Ile Phe Cys Tyr		290		(2) INFORMATION FOR SEQ ID NO:61:		(i) SEQUENCE CHARACTERISTICS:		(A) LENGTH: 284 amino acids		(B) TYPE: amino acid	15	(C) STRANDEDNESS: single		(D) TOPOLOGY: linear		(ii) MOLECULE TYPE: peptide		(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:	20	Leu Leu Phe Leu Leu Phe Leu Ile Met Tyr Leu Ala Thr Val Leu Gly		1	5		10		15		Asn Leu Leu Ile Ile Leu Ala Ile Gly Gly Asp Ser Arg Leu His Thr		20	25		30		Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe		35	40		45	25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser		50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly														
	265		270		Pro Pro Ser Leu Leu His Phe Phe Leu Val Leu Cys His Leu Pro Cys		275		280		285	10	Phe Ile Phe Cys Tyr		290		(2) INFORMATION FOR SEQ ID NO:61:		(i) SEQUENCE CHARACTERISTICS:		(A) LENGTH: 284 amino acids		(B) TYPE: amino acid	15	(C) STRANDEDNESS: single		(D) TOPOLOGY: linear		(ii) MOLECULE TYPE: peptide		(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:	20	Leu Leu Phe Leu Leu Phe Leu Ile Met Tyr Leu Ala Thr Val Leu Gly		1	5		10		15		Asn Leu Leu Ile Ile Leu Ala Ile Gly Gly Asp Ser Arg Leu His Thr		20	25		30		Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe		35	40		45	25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser		50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																
	270																																																																																																																																																									
	Pro Pro Ser Leu Leu His Phe Phe Leu Val Leu Cys His Leu Pro Cys																																																																																																																																																									
	275		280		285	10	Phe Ile Phe Cys Tyr		290		(2) INFORMATION FOR SEQ ID NO:61:		(i) SEQUENCE CHARACTERISTICS:		(A) LENGTH: 284 amino acids		(B) TYPE: amino acid	15	(C) STRANDEDNESS: single		(D) TOPOLOGY: linear		(ii) MOLECULE TYPE: peptide		(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:	20	Leu Leu Phe Leu Leu Phe Leu Ile Met Tyr Leu Ala Thr Val Leu Gly		1	5		10		15		Asn Leu Leu Ile Ile Leu Ala Ile Gly Gly Asp Ser Arg Leu His Thr		20	25		30		Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe		35	40		45	25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser		50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																						
	280		285	10	Phe Ile Phe Cys Tyr		290		(2) INFORMATION FOR SEQ ID NO:61:		(i) SEQUENCE CHARACTERISTICS:		(A) LENGTH: 284 amino acids		(B) TYPE: amino acid	15	(C) STRANDEDNESS: single		(D) TOPOLOGY: linear		(ii) MOLECULE TYPE: peptide		(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:	20	Leu Leu Phe Leu Leu Phe Leu Ile Met Tyr Leu Ala Thr Val Leu Gly		1	5		10		15		Asn Leu Leu Ile Ile Leu Ala Ile Gly Gly Asp Ser Arg Leu His Thr		20	25		30		Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe		35	40		45	25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser		50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																								
	285																																																																																																																																																									
10	Phe Ile Phe Cys Tyr																																																																																																																																																									
	290																																																																																																																																																									
	(2) INFORMATION FOR SEQ ID NO:61:																																																																																																																																																									
	(i) SEQUENCE CHARACTERISTICS:																																																																																																																																																									
	(A) LENGTH: 284 amino acids																																																																																																																																																									
	(B) TYPE: amino acid																																																																																																																																																									
15	(C) STRANDEDNESS: single																																																																																																																																																									
	(D) TOPOLOGY: linear																																																																																																																																																									
	(ii) MOLECULE TYPE: peptide																																																																																																																																																									
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:																																																																																																																																																									
20	Leu Leu Phe Leu Leu Phe Leu Ile Met Tyr Leu Ala Thr Val Leu Gly																																																																																																																																																									
	1	5		10		15		Asn Leu Leu Ile Ile Leu Ala Ile Gly Gly Asp Ser Arg Leu His Thr		20	25		30		Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe		35	40		45	25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser		50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																		
	10		15		Asn Leu Leu Ile Ile Leu Ala Ile Gly Gly Asp Ser Arg Leu His Thr		20	25		30		Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe		35	40		45	25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser		50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																					
	15																																																																																																																																																									
	Asn Leu Leu Ile Ile Leu Ala Ile Gly Gly Asp Ser Arg Leu His Thr																																																																																																																																																									
	20	25		30		Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe		35	40		45	25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser		50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																											
	30																																																																																																																																																									
	Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe																																																																																																																																																									
	35	40		45	25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser		50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																		
	45																																																																																																																																																									
25	Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser																																																																																																																																																									
	50	55		60		Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala		65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																									
	60																																																																																																																																																									
	Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala																																																																																																																																																									
	65	70		75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																
	75		80	30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp		85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																			
	80																																																																																																																																																									
30	Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp																																																																																																																																																									
	85	90		95		Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln		100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																									
	95																																																																																																																																																									
	Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln																																																																																																																																																									
	100	105		110		Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.		115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																																
	110																																																																																																																																																									
	Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn.																																																																																																																																																									
	115	120		125	35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp		130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																																							
	125																																																																																																																																																									
35	Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp																																																																																																																																																									
	130	135		140		Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys		145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																																														
	140																																																																																																																																																									
	Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys																																																																																																																																																									
	145	150		155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																																																					
	155		160	40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val		165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																																																								
	160																																																																																																																																																									
40	Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val																																																																																																																																																									
	165	170		175		Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile		180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																																																														
	175																																																																																																																																																									
	Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile																																																																																																																																																									
	180	185		190		Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser		195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																																																																					
	190																																																																																																																																																									
	Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser																																																																																																																																																									
	195	200		205	45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly		210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																																																																												
	205																																																																																																																																																									
45	Phe Ser Thr Cys Cly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly																																																																																																																																																									
	210		215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																																																																																			
	215		220		Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																																																																																					
	220																																																																																																																																																									
	Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly																																																																																																																																																									

- 117 -

225	230	235	240
-----	-----	-----	-----

Arg Asp Met Ala Ala Ala Val Met Tyr Ala Val Val Thr Pro Met Ile			
245	250	255	

5	Asn Pro Phe Ile Tyr Ser Leu Arg Asn Ser Asp Met Lys Ala Ala Leu		
	260	265	270

Arg Lys Val Leu Ala Met Arg Phe Pro Ser Lys Gln			
275	280		

## (2) INFORMATION FOR SEQ ID NO:62:

## (i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 277 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Leu Leu Phe Leu Leu Phe Leu Val Met Tyr Leu Leu Thr Val Val Gly			
1	5	10	15

Asn Leu Ala Ile Ile Ser Leu Val Gly Ala His Arg Cys Leu Gln Pro			
20	25	30	

20	His Thr Pro Met Tyr Phe Phe Leu Cys Asn Leu Ser Phe Leu Glu Ile		
	35	40	45

Trp Phe Thr Thr Ala Cys Val Pro Lys Thr Leu Ala Thr Phe Ala Pro			
50	55	60	

25	Arg Gly Gly Val Ile Ser Leu Ala Gly Cys Ala Thr Lys Tyr Phe Val		
	65	70	80

Phe Ser Leu Gly Cys Thr Glu Tyr Phe Leu Leu Ala Val Met Ala Tyr			
85	90	95	

Asp Arg Tyr Leu Ala Ile Cys Leu Pro Leu Arg Tyr Gly Gly Ile Met			
100	105	110	

30	Arg Pro Gly Ile Ala Met Arg Leu Ala Leu Gly Ser Trp Leu Cys Gly		
	115	120	125

Phe Ser Ala Ile Thr Val Pro Ala Thr Leu Ile Ala Arg Leu Ser Phe			
130	135	140	

35	Cys Gly Ser Arg Val Ile Asn His Phe Phe Cys Asp Ile Ser Pro Trp		
	145	150	160

Ile Val Leu Ser Cys Thr Asp Thr Gln Val Val Glu Leu Val Ser Phe			
165	170	175	

Gly Ile Ala Phe Cys Val Ile Leu Gly Ser Cys Gly Ile Thr Leu Val			
180	185	190	

40	Ser Tyr Ala Lys Ile Pro Ser Ala Arg Gly Arg His Arg Ala Phe Ser		
	195	200	205

Thr Cys Ser Ser His Leu Thr Val Val Leu Ile Trp Tyr Gly Ser Thr			
210	215	220	

45	Ile Phe Leu His Val Arg Thr Ser Val Glu Ser Ser Leu Asp Leu Thr		
	225	230	240

Lys Ala Ile Thr Val Leu Asn Thr Ile Val Thr Pro Val Leu Asn Pro			
---	--	--	--

- 118 -

245	250	255
-----	-----	-----

Phe Ile Tyr Thr Leu Arg Asn Lys Asp Val Lys Glu Ala Leu Arg Arg	260	265
---	-----	-----

5	Thr Val Lys Gly Lys	
---	---------------------	--

## (2) INFORMATION FOR SEQ ID NO:63:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 273 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(iii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Leu Ile Phe Ala Leu Phe Leu Ser Met Tyr Leu Val Thr Val Leu Gly	15	15
---	----	----

Asn Leu Leu Ile Ile Met Ala Ile Ile Thr Gln Ser His Leu His Thr	20	25
---	----	----

Pro Met Tyr Phe Phe Leu Ser Phe Val Asp Ile Cys Phe Thr Ser Thr	35	40
---	----	----

20	Thr Ile Pro Leu Val Asn Ile Tyr Thr Gln Ser Lys Ser Ile Thr Tyr	50
----	---	----

Glu Asp Cys Ile Ser Leu Val Phe Ala Glu Leu Gly Asn Phe Leu Leu	65	75
---	----	----

25	Ala Val Met Ala Tyr Asp Arg Tyr Val Ala Xaa Cys His Pro Leu Cys	85
----	---	----

Tyr Thr Val Ile Val Asn His Arg Leu Cys Ile Leu Leu Leu Leu	100	105
---	-----	-----

Ser Trp Val Ile Ser Ile Phe Arg Ala Phe Ile Gln Ser Leu Ile Val	115	120
---	-----	-----

30	Leu Gln Leu Thr Phe Cys Gly Asp Val Lys Ile Pro His Phe Phe Cys	130
----	---	-----

135	140	
-----	-----	--

35	Glu Leu Asn Gln Leu Ser Gln Leu Thr Cys Ser Asp Asn Phe Pro Ser	145
----	---	-----

His Leu Ile Met Asn Leu Val Pro Val Met Leu Ala Ala Ile Ser Phe	165	170
---	-----	-----

175	180	185
-----	-----	-----

190	195	200
-----	-----	-----

40	Tyr Lys Ala Phe Ser Thr Cys Ala Ser His Leu Ser Ile Val Ser Leu	210
----	---	-----

215	220	
-----	-----	--

225	230	235
-----	-----	-----

240	245	250
-----	-----	-----

240	260	265
-----	-----	-----

- 119 -

Gly

(2) INFORMATION FOR SEQ ID NO:64:

- (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 269 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Leu Phe Tyr Ala Leu Phe Leu Val Met Tyr Leu Thr Thr Ile Leu Gly  
1 5 10 15

Asn Leu Leu Ile Ile Val Leu Val Gln Leu Asp Ser Gln Leu His Thr  
20 25 30

15 Pro Met Tyr Leu Phe Leu Ser Asn Leu Ser Phe Ser Asp Leu Cys Phe  
35 40 45

Ser Ser Leu Lys Leu Leu Gln Asn Met Arg Ser Gln Asp Thr Ser Ile  
50 55 60

20 Pro Tyr Gly Gly Cys Leu Ala Gln Thr Tyr Phe Phe Met Val Phe Gly  
           65              70              75              80

Asp Leu Ser Phe Leu Leu Val Ala Met Ala Tyr Asp Arg Tyr Val Ala  
85 90 95

Ile Cys Phe Leu Pro His Tyr Thr Ser Ile Met Ser Pro Lys Leu Cys  
100 105 110

25           Thr Cys Leu Val Leu Leu Leu Trp Met Leu Thr Thr Ser His Met Met  
              115                   120                   125

Thr Leu Leu Ala Ala Arg Leu Ser Phe Cys Glu Asn Asn Trp Leu Asn  
130 135 140

30 Phe Phe Cys Asp Leu Phe Val Leu Leu Lys Ile Ala Cys Ser Asp Thr  
 145 150 155 160

Tyr Ile Asn Glu Leu Phe Ile Met Ser Thr Leu Leu Ile Ile Ile Pro  
165 170 175

Phe Phe Leu Ile Val Met Ser Tyr Ala Lys Val Pro Ser Thr Gln Gly  
180 185 190

35 Ile Cys Lys Val Phe Ser Thr Cys Gly Ser His Leu Ser Val Val Ser  
195 200 205

Leu Phe Tyr Gly Thr Ile Ile Gly Leu Tyr Leu Cys Pro Ala Gly Asn  
210 215 220

Asn Ser Thr Val Lys Glu Met Val Met Ala Met Met Tyr Thr Val Val  
40 225 230 235 240

Thr Pro Met Ile Asn Pro Phe Ile Tyr Ser Leu Arg Asn Arg Asp Leu  
245 250 255

Arg Ala Leu Ile Arg Val Ile Cys Ser Met Ile Thr Leu

45 (2) INFORMATION FOR SEQ ID NO:65:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 286 amino acids  
    (B) TYPE: amino acid

- 120 -

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

5           Leu Leu Phe Phe Leu Ser Leu Leu Xaa Tyr Val Leu Val Leu Thr Glu  
        1                       5                   10                   15  
        Asn Met Leu Ile Ile Ile Ala Ile Arg Asn His Pro Thr Leu His Lys  
        20                      25                      30

10          Pro Met Tyr Phe Phe Leu Phe Leu Glu Ile Trp Tyr Val Thr Val Thr  
        35                      40                      45

15          Ile Pro Lys Leu Met Gly Phe Ile Gly Ser Lys Glu Asn His Gly Gln  
        50                      55                      60

20          Leu Ile Ser Phe Phe Ala Cys Met Thr Gln Leu Tyr Phe Phe Leu Gly  
        65                      70                      75                   80

25          Leu Gly Cys Thr Glu Cys Val Leu Leu Ala Val Met Ala Tyr Asp Arg  
        85                      90                      95

30          Tyr Val Ala Ile Cys His Pro Leu His Tyr Pro Val Ile Val Ser Ser  
        100                    105                      110

35          Arg Ile Glx Val Leu Gly Ser Trp Ala Gly Gly Phe Gly Ile Ser Met  
        115                    120                      125

40          Val Lys Val Phe Leu Ile Ser Arg Leu Ser Tyr Cys Gly Pro Asn Thr  
        130                    135                      140

45          Ile Asn His Phe Phe Cys Asp Val Ser Pro Leu Leu Asn Leu Ser Cys  
        145                    150                      155                   160

50          Thr Asp Met Ser Thr Ala Glu Leu Thr Asp Phe Val Ile Ala Ile Phe  
        165                    170                      175

55          Ile Leu Leu Gly Pro Leu Ser Val Thr Gly Ala Ser Tyr Met Arg Ile  
        180                    185                      190

60          Pro Ser Ala Ala Gly Arg His Lys Ala Phe Ser Thr Cys Ala Ser His  
        195                    200                      205

65          Leu Thr Val Val Ile Ile Phe Tyr Ala Ala Ser Ile Phe Ile Tyr Ala  
        210                    215                      220

70          Arg Pro Lys Ala Leu Ser Ala Phe Thr Asp Asn Lys Leu Val Ser Val  
        225                    230                      235                   240

75          Leu Tyr Ala Val Ile Val Pro Leu Phe Asn Pro Ile Ile Tyr Cys Leu  
        245                    250                      255

80          Arg Asn Gln Asp Val Lys Arg Ala Leu Arg Arg Thr Leu His Leu Ala  
        260                    265                      270

85          Gln Asp Gln Glu Ala Asn Thr Asn Lys Gly Ser Lys Ile Gly  
        275                    280                      285

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 275 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

45

- 121 -

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

	Leu	Phe	Phe	Ala	Leu	Phe	Leu	Ile	Met	Tyr	Leu	Thr	Thr	Phe	Leu	Gly
1																15
									5							
5																
	Asn	Leu	Leu	Ile	Val	Val	Leu	Val	Gln	Leu	Asp	Ser	His	Leu	His	Thr
																30
									20							
										25						
	Pro	Met	Tyr	Leu	Phe	Leu	Ser	Asn	Leu	Ser	Phe	Ser	Asp	Leu	Cys	Phe
																45
									35			40				
	Ser	Ser	Val	Thr	Met	Leu	Lys	Leu	Leu	Gln	Asn	Ile	Gln	Ser	Gln	Val
																50
										55						
10																
	Pro	Ser	Ile	Ser	Tyr	Ala	Gly	Cys	Leu	Trp	Ile	Phe	Phe	Leu	Leu	
																80
									65			70				
	Phe	Gly	Tyr	Leu	Gly	Asn	Phe	Leu	Leu	Val	Ala	Met	Ala	Tyr	Asp	Arg
																95
									85			90				
15																
	Tyr	Val	Ala	Ile	Cys	Phe	Pro	Leu	His	Tyr	Thr	Asn	Ile	Met	Ser	His
																110
									100			105				
	Lys	Leu	Cys	Thr	Cys	Leu	Leu	Leu	Val	Phe	Trp	Ile	Met	Arg	Ser	Ser
																125
									115			120				
	His	Ala	Met	Met	Ile	Thr	Leu	Ile	Ala	Ala	Arg	Leu	Ser	Phe	Cys	Glu
																140
20									130			135				
	Asn	Asn	Val	Leu	Leu	Asn	Phe	Phe	Cys	Asp	Leu	Phe	Val	Leu	Leu	Lys
																160
									145			150				
	Leu	Ala	Cys	Ser	Asp	Thr	Tyr	Val	Asn	Glu	Leu	Met	Ile	His	Ile	Met
																175
									165			170				
25																
	Glu	Val	Ile	Ile	Val	Ile	Pro	Phe	Val	Leu	Ile	Val	Ile	Ser	Tyr	
																190
									180			185				
	Ala	Lys	Val	Pro	Ser	Thr	Gln	Ser	Ile	His	Lys	Val	Phe	Ser	Thr	Cys
																205
									195			200				
	Gly	Ser	His	Leu	Ser	Val	Val	Ser	Leu	Phe	Tyr	Gly	Thr	Ile	Ile	Gly
																220
									210			215				
30																
	Leu	Tyr	Leu	Cys	Pro	Ser	Gly	Asp	Asn	Phe	Ser	Leu	Lys	Gly	Ser	Leu
																240
									225			230				
	Thr	Val	Val	Thr	Pro	Ile	Met	Pro	Phe	Ile	Tyr	Ser	Leu	Arg	Asn	Arg
																255
									245			250				
35																
	Asp	Met	Lys	Gln	Ala	Leu	Ile	Arg	Val	Thr	Cys	Ser	Lys	Lys	Ile	Ser
																270
									260			265				
	Leu	Pro	Trp													
									275							

## (2) INFORMATION FOR SEQ ID NO:67:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 284 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## 45 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Leu	Phe	Tyr	Ala	Leu	Phe	Leu	Ala	Met	Tyr	Leu	Thr	Leu	Lys	Gly
1														15
									5			10		

- 122 -

	Asn Leu Ile Ile Ile Ile Leu Ile Leu Leu Asp Ser His Leu His Thr			
	20	25	30	
	Pro Met Tyr Leu Phe Leu Ser Asn Leu Ser Phe Ala Asp Leu Cys Phe			
	35	40	45	
5	Ser Ser Leu Lys Leu Leu Gln Asn Met Gln Ser Gln Val Pro Ser Ile			
	50	55	60	
	Pro Tyr Ala Gly Cys Leu Ala Gln Ile Tyr Phe Phe Leu Phe Phe Gly			
	65	70	75	80
10	Asp Leu Gly Asn Phe Leu Leu Val Ala Met Ala Tyr Asp Arg Tyr Val			
	85	90	95	
	Ala Ile Cys Phe Pro Leu His Tyr Met Ser Ile Met Ser Pro Lys Ile			
	100	105	110	
	Glx Val Ser Leu Val Val Leu Ser Trp Val Leu Thr Thr Phe His Ala			
	115	120	125	
15	Met Leu His Thr Leu Ile Met Ala Arg Leu Ser Phe Cys Glu Asp Ser			
	130	135	140	
	Val Ile Pro His Tyr Phe Cys Asp Met Ser Thr Leu Leu Lys Val Ala			
	145	150	155	160
20	Cys Ser Asp Thr His Asp Asn Glu Leu Ala Ile Phe Ile Leu Gly Gly			
	165	170	175	
	Pro Ile Val Val Leu Pro Phe Leu Leu Ile Ile Val Ser Tyr Ala Arg			
	180	185	190	
	Ile Val Ser Ser Ile Phe Lys Val Pro Ser Ser Gln Ser Ile His Lys			
	195	200	205	
25	Ala Phe Ser Thr Cys Gly Ser His Leu Ser Val Val Ser Leu Phe Tyr			
	210	215	220	
	Gly Thr Val Ile Gly Leu Tyr Leu Cys Pro Ser Ala Asn Asn Ser Glu			
	225	230	235	240
30	Val Lys Glu Thr Val Met Ser Ile Tyr Thr Met Val Pro Met Leu Asn			
	245	250	255	
	Pro Phe Ile Tyr Ser Leu Arg Asn Arg Asp Ile Lys Asp Ala Leu Glu			
	260	265	270	
	Lys Ile Met Cys Lys Lys Gln Ile Pro Ser Phe Leu			
	275	280		
35	(2) INFORMATION FOR SEQ ID NO:68:			
	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 277 amino acids			
	(B) TYPE: amino acid			
	(C) STRANDEDNESS: single			
40	(D) TOPOLOGY: linear			
	(ii) MOLECULE TYPE: peptide			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:			
	Leu Phe Tyr Ala Leu Phe Leu Ala Met Tyr Leu Thr Ile Ile Leu Gly			
	1	5	10	15
45	Asn Leu Leu Il Ile Val Leu Val Arg Leu Asp Ser His Leu His Met			
	20	25	30	

- 123 -

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 274 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:  
Val Phe Tyr Ala Leu Phe Leu Ser Met Tyr Leu Thr Ile Val Leu Gly  
1 5 10 15

Asn Leu Ile Ile Ile Leu Ile His Leu Asp Ser His Leu His Thr  
20 25 30

45 Pro Met Tyr Leu Phe Leu Ser Asn Leu Ser Phe Ser Asp Leu Cys Phe  
35 40 45

- 124 -

Ser Ser Leu Lys Leu Leu Gln Asn Met Gln Ser Gln Val Pro Ser Ile  
 50 55 60

Pro Phe Ala Gly Cys Leu Thr Gln Leu Tyr Phe Tyr Leu Tyr Phe Ala  
 65 70 75 80

5 Asp Leu Glu Ser Phe Leu Leu Val Ala Met Ala Tyr Asp Arg Tyr Val  
 85 90 95

Ala Ile Cys Phe Pro Leu His Tyr Met Ser Ile Met Ser Pro Lys Leu  
 100 105 110

10 Cys Val Ser Leu Trp Leu Ser Trp Val Leu Thr Thr Phe His Ala Met  
 115 120 125

Leu His Thr Leu Ile Met Ala Arg Leu Ser Phe Cys Ala Asp Leu Pro  
 130 135 140

His Phe Phe Cys Asp Ile Ser Pro Leu Leu Lys Leu Ser Cys Ser Asp  
 145 150 155 160

15 Thr His Val Asn Glu Leu Val Ile Phe Leu Gly Leu Val Ile Val Ile  
 165 170 175

Pro Phe Val Leu Ile Ile Val Ser Tyr Ala Arg Val Val Ala Ser Ile  
 180 185 190

20 Leu Lys Val Pro Ser Val Arg Gly Ile His Lys Ile Phe Ser Thr Cys  
 195 200 205

Gly Ser His Leu Ser Val Val Ser Leu Phe Tyr Gly Thr Ile Ile Gly  
 210 215 220

Leu Tyr Leu Cys Pro Ser Ala Asn Asn Ser Thr Val Lys Glu Thr Leu  
 225 230 235 240

25 Thr Val Val Thr Pro Leu Pro Phe Ile Tyr Ser Leu Arg Asn Arg Asp  
 245 250 255

Met Lys Glu Ala Leu Ile Arg Val Leu Cys Lys Lys Lys Ile Thr Phe  
 260 265 270

Cys Leu

30 (2) INFORMATION FOR SEQ ID NO:70:  
 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 345 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:  
 Leu Ala Ile Ala Val Leu Ser Leu Thr Leu Leu Gly Thr Phe Thr Val  
 40 1 5 10 15

Leu Glu Asn Leu Leu Val Leu Cys Val Ile Leu His Ser Arg Ser Leu  
 20 25 30

Arg Cys Arg Pro Ser Tyr His Phe Ile Gly Ser Leu Ala Val Ala Asp  
 35 40 45

45 Leu Leu Gly Ser Val Ile Phe Val Tyr Ser Phe Val Asp Phe His Val  
 50 55 60

Phe His Arg Lys Asp Ser Pro Asn Val Phe Leu Phe Lys Leu Gly Gly  
 65 70 75 80

- 125 -

	Val Thr Ala Ser Phe Thr Ala Ser Val Gly Ser Leu Phe Leu Thr Ala
	85 90 95
	Ile Asp Arg Tyr Ile Ser Ile His Pro Pro Ile Ala Tyr Lys Arg Ile
	100 105 110
5	Val Arg Arg Pro Lys Ala Val Val Ala Phe Cys Leu Met Thr Ile Ala
	115 120 125
	Ile Val Ile Ala Val Leu Pro Leu Leu Gly Trp Asn Cys Lys Lys Leu
	130 135 140
10	Gln Ser Val Cys Cys Asp Ile Phe Pro Leu Ile Asp Gly Thr Tyr Leu
	145 150 155 160
	Met Phe Trp Ile Gly Val Thr Ser Val Leu Leu Leu Phe Ile Val Tyr
	165 170 175
	Ala Tyr Met Tyr Ile Leu Trp Lys Ala His Ser His Ala Val Arg Ala
	180 185 190
15	Gln Arg Gly Thr Gln Lys Ser Ile Ile Ile His Thr Ser Glu Asp Gly
	195 200 205
	Lys Val Gln Val Thr Arg Pro Asp Gln Ala Arg Met Asp Ile Arg Leu
	210 215 220
20	Ala Lys Thr Leu Val Leu Ile Leu Val Val Leu Ile Ile Cys Trp Gly
	225 230 235 240
	Pro Leu Leu Ala Ile Met Val Tyr Asp Val Phe Gly Leu Leu Ile Lys
	245 250 255
	Thr Val Phe Ala Phe Cys Ser Leu Leu Ile Asn Ser Thr Val Asn Pro
	260 265 270
25	Ile Ile Tyr Ala Leu Arg Ser Lys Asp Leu Arg His Ala Phe Arg Ser
	275 280 285
	Trp Pro Ser Cys Glu Gly Thr Ala Gln Pro Leu Asp Asn Ser Met Gly
	290 295 300
30	Asp Ser Asp Cys Leu His Lys His Ala Asn Asn Thr Ala Ser Met His
	305 310 315 320
	Arg Ala Ala Glu Ser Cys Ile Lys Ser Thr Val Lys Leu Ala Leu Val
	325 330 335
	Ser Thr Asp Thr Ser Ala Glu Ala Leu
	340 345
35	(2) INFORMATION FOR SEQ ID NO:71:
	(i) SEQUENCE CHARACTERISTICS:
	(A) LENGTH: 349 amino acids
	(B) TYPE: amino acid
	(C) STRANDEDNESS: single
40	(D) TOPOLOGY: linear
	(ii) MOLECULE TYPE: peptide
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

	Lys Ala Leu Leu Ile Val Ala Tyr Ser Phe Thr Ile Val Phe Ser Leu
	1 5 10 15
45	Phe Gly Asn Val Leu Val Cys His Tyr Ile Phe Lys Asn Gln Arg Lys
	20 25 30

- 126 -

	Ile Ser Ala Thr Ser Leu Phe Ile Val Asn Leu Ala Val Ala Asp Ile
	35 40 45
	Ile Glu Thr Leu Leu Asn Thr Pro Phe Thr Leu Val Arg Phe Val Asn
	50 55 60
5	Ser Thr Trp Tyr Phe Gly Lys Gly Met Leu His Val Ser Arg Phe Ala
	65 70 75 80
	Gln Tyr Cys Ser Leu His Val Ser Ala Leu Ile Leu Thr Ala Ile Ala
	85 90 95
10	Val Asp Arg His Gln Val Ile Met Pro Leu Lys Pro Arg Ile Ser Ile
	100 105 110
	Thr Lys Gly Val Ile Tyr Ile Ala Val Ile Trp Val Met Thr Phe Phe
	115 120 125
	Ser Leu Pro His Ala Ile Cys Gln Lys Leu Phe Thr Phe Lys Tyr Ser
	130 135 140
15	Glu Asp Ile Val Arg Ser Leu Cys Leu Asp Pro Phe Pro Glu Pro Ala
	145 150 155 160
	Asp Leu Phe Trp Lys Tyr Leu Asp Ile Ala Thr Phe Ile Leu Leu Tyr
	165 170 175
20	Leu Leu Pro Leu Phe Ile Ile Ser Val Ala Tyr Ala Arg Val Ala Lys
	180 185 190
	Lys Leu Trp Leu Cys Asn Thr Ile Gly Asp Val Thr Thr Glu Gln Tyr
	195 200 205
	Leu Ala Leu Arg Arg Lys Lys Lys Thr Thr Val Lys Met Leu Val Leu
	210 215 220
25	Val Val Val Leu Phe Ala Leu Cys Trp Phe Pro Leu Asn Cys Tyr Val
	225 230 235 240
	Leu Leu Leu Ser Ser Lys Ala Ile His Thr Asn Asn Ala Leu Tyr Phe
	245 250 255
30	Ala Phe His Trp Phe Ala Met Ser Ser Thr Cys Tyr Asn Pro Phe Ile
	260 265 270
	Tyr Cys Trp Leu Asn Glu Asn Phe Arg Val Glu Leu Lys Ala Leu Leu
	275 280 285
	Ser Met Gln Pro Pro Pro Lys Pro Glu Asp Arg Leu Pro Ser Pro Val
	290 295 300
35	Pro Ser Phe Arg Val Ala Trp Thr Glu Lys Ser His Gly Arg Arg Ala
	305 310 315 320
	Pro Leu Pro Asn His His Leu Pro Ser Ser Gln Ile Gln Ser Gly Lys
	325 330 335
40	Thr Asp Leu Ser Ser Val Glu Pro Val Val Ala Met Ser
	340 345

- (2) INFORMATION FOR SEQ ID NO:72:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 301 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

- 127 -

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

	Ile Phe Thr Ile Ala Leu Ala Tyr Gly Ala Val Ile Ile Leu Gly Val	
1	5	10
	15	
5	Ser Gly Asn Leu Ala Leu Ile Ile Ile Leu Lys Gln Lys Glu Leu	
	20	25
	30	
	Ile Leu Ile Val Asn Leu Ser Phe Ser Asp Leu Leu Val Ala Val Trp	
	35	40
	45	
	Leu Pro Phe Thr Phe Val Tyr Thr Leu Ile Cys His Trp Val Phe Gly	
	50	55
	60	
10	Glu Cys Cys Lys Leu Asn Pro Phe Val Gln Cys Val Ser Ile Thr Val	
	65	70
	75	80
	Ser Ile Phe Ser Leu Val Leu Ile Ala Val Glu Arg His Gl.. Leu Ile	
	85	90
	95	
15	Ile Asn Pro Arg Gly Trp Arg Pro Asn Asn Arg His Ala Tyr Ile Gly	
	100	105
	110	
	Ile Thr Val Ile Trp Val Ile Ala Val Ala Ser Ser Leu Pro Phe Val	
	115	120
	125	
	Ile Tyr Gln Ile Leu Thr Asp Glu Pro Phe Gln Asn Val Ser Leu Ala	
	130	135
	140	
20	Ala Phe Lys Asp Lys Tyr Val Cys Phe Asp Lys Phe Pro Ser Asp Ser	
	145	150
	155	160
	His Arg Leu Ser Tyr Thr Leu Leu Leu Val Leu Gln Tyr Phe Gly	
	165	170
	175	
25	Pro Leu Cys Phe Ile Phe Ile Cys Tyr Phe Lys Ile Tyr Ile Arg Leu	
	180	185
	190	
	Lys Arg Arg Asn Asn Met Met Lys Ile Arg Asp Ser Lys Tyr Arg Ser	
	195	200
	205	
	Ser Glu Thr Lys Arg Ile Asn Val Met Leu Leu Ser Ile Val Val Ala	
	210	215
	220	
30	Phe Ala Val Cys Trp Leu Pro Leu Thr Ile Phe Asn Ile Val Phe Asp	
	225	230
	235	240
	Trp Asn His Gln Ile Ile Ala Thr Cys Asn His Asn Leu Leu Phe Leu	
	245	250
	255	
35	Leu Cys His Leu Thr Leu Ser Thr Cys Val Asn Pro Ile Phe Tyr Gly	
	260	265
	270	
	Phe Leu Asn Lys Asn Phe Gln Arg Asp Leu Gln Phe Phe Phe Asn Phe	
	275	280
	285	
	Cys Asp Phe Arg Ser Arg Asp Gly Arg Thr Thr Arg Leu	
	290	295
	300	

## 40 (2) INFORMATION FOR SEQ ID NO:73:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 334 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

45 (ii) MOLECULE TYPE: peptide

- 128 -

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

	Leu Thr Ser Val Val Phe Ile Leu Ile Cys Cys Phe Ile Ile Leu Glu
1	5 10 15
5	Asn Ile Phe Val Leu Leu Thr Ile Trp Lys Thr Lys Lys Phe His Arg 20. 25 30
	Pro Met Tyr Tyr Phe Ile Gly Asn Ile Ala Leu Ser Asp Leu Ile Ala 35 40 45
	Gly Val Ala Tyr Thr Ala Asn Leu Leu Leu Ser Gly Ala Thr Thr Tyr 50 55 60
10	Lys Leu Thr Pro Ala Gln Trp Phe Leu Arg Glu Gly Ser Met Phe Val 65 70 75 80
	Ala Leu Ser Leu Ser Val Phe Ser Leu Leu Ala Ile Ala Ile Glu Arg 85 90 95
15	Tyr Ile Thr Met Leu Lys Met Leu His Asn Gly Ser Asn Asn Phe Arg 100 105 110
	Leu Phe Leu Leu Ile Ser Ala Cys Trp Val Ile Ser Leu Ile Leu Gly 115 120 125
	Gly Leu Pro Ile Met Gly Trp Asn Cys Ile Ser Ala Leu Ser Ser Cys 130 135 140
20	Ser Thr Val Leu Pro Leu Tyr His Lys His Tyr Ile Leu Phe Cys Thr 145 150 155 160
	Leu Ile Val Phe Thr Leu Leu Leu Ser Ile Val Ile Leu Tyr Cys 165 170 175
25	Arg Ile Tyr Ser Leu Val Arg Thr Arg Ser Arg Arg Leu Thr Phe Arg 180 185 190
	Lys Asn Ile Ser Lys Ala Ser Arg Ser Ser Glu Asn Val Ala Leu Leu 195 200 205
	Lys Thr Val Ile Ile Val Leu Ser Val Phe Ile Ala Cys Trp Ala Pro 210 215 220
30	Leu Phe Ile Leu Leu Leu Asp Val Gly Cys Lys Val Lys Thr Cys 225 230 235 240
	Asp Ile Leu Phe Arg Ala Glu Tyr Phe Leu Val Ile Ala Val Ile Asn 245 250 255
35	Ser Gly Thr Asn Pro Ile Ile Tyr Thr Leu Thr Asn Lys Glu Met Arg 260 265 270
	Arg Ala Phe Ile Arg Ile Met Cys Cys Lys Cys Pro Ser Gly Asp Ser 275 280 285
	Ala Gly Lys Phe Lys Arg Pro Ile Ile Ala Gly Met Glu Phe Ser Arg 290 295 300
40	Ser Lys Ser Asp Asn Ser Ser His Pro Gln Lys Asp Glu Gly Asp Asn 305 310 315 320
	Pro Glu Thr Ile Met Ser Ser Gly Asn Val Asn Ser Ser Ser 325 330

(2) INFORMATION FOR SEQ ID NO:74:  
 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 236 amino acids

- 129 -

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:  
 Ile Thr Tyr Tyr Ile Leu Ile Gly Leu Cys Ala Val Val Gly Asn Ile  
 1                       5                       10                       15

Leu Leu Val Ile Trp Val Val Lys Leu Asn Arg Thr Leu Arg Thr Thr  
 20                      25                      30

10 Thr Phe Tyr Phe Ile Val Ser Ile Ala Leu Ala Asp Ile Ala Val Leu  
 35                      40                      45

Val Ile Pro Leu Ala Ile Ala Ser Ala Trp Arg Ser Arg Cys Thr Ser  
 50                      55                      60

15 Asn Cys Leu Phe Met Ser Cys Val Leu Leu Val Phe Thr His Ala Ser  
 65                      70                      75                      80

Ile Met Ser Leu Leu Ala Ile Ala Val Asp Arg Tyr Leu Arg Val Lys  
 85                      90                      95

Leu Thr Val Arg Tyr Arg Thr Val Thr Thr Gln Arg Arg Ile Trp Leu  
 100                    105                      110

20 Phe Leu Gly Leu Cys Trp Leu Val Ser Phe Leu Val Gly Leu Thr Pro  
 115                    120                      125

Trp Gly Trp Asn Arg Lys Val Thr Leu Glu Leu Ser Gln Asn Ser Ser  
 130                    135                      140

25 Thr Leu Arg Glu Phe Lys Thr Pro Lys Ser Leu Phe Leu Val Leu Phe  
 145                    150                      155                      160

Leu Phe Ala Leu Cys Trp Leu Pro Leu Ser Ile Ile Asn Phe Val Ser  
 165                    170                      175

Tyr Phe Asn Val Lys Ile Pro Glu Thr Leu Leu Gly Ile Leu Ser  
 180                    185                      190

30 His Ala Asn Ser Leu Pro Ile Val Tyr Ala Cys Lys Lys Phe Lys  
 195                    200                      205

Glu Thr Tyr Phe Val Ile Leu Arg Ala Cys Arg Leu Cys Gln Thr Ser  
 210                    215                      220

35 Asp Ser Leu Asp Ser Asn Leu Glu Gln Thr Thr Glu  
 225                    230                      235

(2) INFORMATION FOR SEQ ID NO:75:  
 (i) SEQUENCE CHARACTERISTICS:  

- (A) LENGTH: 322 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:  
Ala Ile Leu Ile Ser Phe Ile Tyr Ser Trp Cys Leu Val Gly Leu Cys

45                    1                      5                      10                      15

Gly Asn Ser Met Val Ile Tyr Val Ile Leu Arg Tyr Ala Ly- Met Lys  
 20                    25                      30

Thr Ala Thr Asn Ile Tyr Ile Leu Asn Ile Ala Ile Ala Asp Glu Leu

- 130 -

	35	40	45
	Leu Val Pro Phe Leu Val Thr Ser Thr Leu Leu Arg His Trp Pro Phe		
	50	55	60
5	Gly Ala Leu Leu Cys Arg Leu Val Leu Ser Val Asp Ala Val Asn Met		
	65	70	75
	Phe Thr Ser Ile Tyr Cys Leu Thr Val Leu Ser Val Asp Arg Tyr Val		
	85	90	95
	Ala Val Val His Pro Ile Lys Ala Ala Arg Tyr Arg Arg Pro Thr Val		
	100	105	110
10	Ala Lys Val Val Asn Leu Gly Val Trp Val Leu Ser Leu Leu Val Ile		
	115	120	125
	Leu Pro Ile Trp Phe Ser Arg Thr Ala Ala Asn Ser Asp Gly Thr Val		
	130	135	140
15	Ala Cys Asn Met Ile Trp Glu Pro Ala Gln Phe Trp Leu Va. Gly Phe		
	145	150	155
	Val Leu Tyr Thr Phe Leu Met Phe Leu Leu Pro Val Gly Ala Ile Cys		
	165	170	175
	Leu Cys Tyr Val Leu Ile Ile Ala Lys Met Arg Met Val Ala Leu Lys		
	180	185	190
20	Ala Gly Trp Gln Gln Arg Lys Arg Ser Glu Arg Lys Ile Thr Leu Val		
	195	200	205
	Met Met Val Val Met Val Phe Val Ile Cys Trp Phe Tyr Val Val Gln		
	210	215	220
25	Leu Val Asn Val Phe Ala Glu Gln Asp Asp Ala Thr Val Ser Gln Leu		
	225	230	235
	Ser Val Ile Leu Gly Tyr Ala Asn Ser Cys Ala Asn Pro Ile Leu Tyr		
	245	250	255
	Gly Phe Leu Ser Asp Asn Phe Lys Arg Ser Phe Gln Arg Ile Leu Cys		
	260	265	270
30	Leu Ser Leu Asn Ala Ala Glu Glu Pro Val Asp Tyr Tyr Ala Thr Ala		
	275	280	285
	Leu Lys Ser Arg Ala Tyr Ser Val Glu Asp Phe Gln Pro Glu Asn Leu		
	290	295	300
35	Glu Ser Gly Gly Val Phe Arg Asn Cys Thr Cys Ala Ser Arg Ile Ser		
	305	310	315
	Thr Leu		

- (2) INFORMATION FOR SEQ ID NO:76:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 298 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptid
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:
- Val Thr Asn Tyr Ile Phe Leu Leu Leu Cys Leu Cys Gly Leu Val Gly  
1                   5                   10                   15

- 131 -

	Asn Gly Leu Val Leu Trp Phe Phe Gly Phe Ser Ile Lys Arg Thr Pro			
	20	25	30	
	Phe Ser Ile Tyr Ile Tyr Phe Leu His Ile Ala Ser Ala Asp Gly Ile			
	35	40	45	
5	Tyr Leu Phe Ser Lys Ala Val Ile Ala Leu Leu Asn Met Gly Thr Phe			
	50	55	60	
	Leu Gly Ser Phe Pro Asp Tyr Val Arg Arg Val Ser Arg Ile Val Gly			
	65	70	75	80
10	Leu Thr Phe Phe Ala Gly Val Ser Leu Leu Pro Ala Ile Ser Ile Glu			
	85	90	95	
	Arg Cys Val Ser Val Ile Phe Pro Met Trp Tyr Trp Arg Arg Arg Pro			
	100	105	110	
	Lys Arg Leu Ser Ala Gly Val Cys Ala Leu Leu Trp Leu Leu Ser Phe			
	115	120	125	
15	Leu Val Thr Ser Ile His Asn Tyr Phe Cys Leu Leu Gly His Glu Ala			
	130	135	140	
	Ser Gly Thr Ala Cys Leu Asn Met Asp Ile Ser Leu Leu Gly Ile Leu			
	145	150	155	160
20	Leu Phe Phe Leu Phe Cys Pro Ile Met Val Leu Pro Cys Ile Ala Leu			
	165	170	175	
	Leu His Val Glu Cys Arg Ala Arg Arg Gln Arg Ser Ala Lys Leu			
	180	185	190	
	Asn His Val Val Leu Ala Ile Val Ser Val Phe Leu Val Ser Ser Ile			
	195	200	205	
25	Tyr Leu Gly Ile Asp Trp Phe Leu Phe Trp Val Phe Gln Ile Pro Ala			
	210	215	220	
	Pro Phe Pro Glu Tyr Val Arg Asp Leu Cys Ile Cys Ile Asn Ser Ser			
	225	230	235	240
30	Ala Lys Pro Ile Val Tyr Phe Ile Ala Gly Arg Asp Lys Ser Gln Arg			
	245	250	255	
	Leu Trp Glu Pro Leu Arg Val Val Phe Gln Arg Ala Leu Arg Asp Gly			
	260	265	270	
	Ala Glu Pro Gly Asp Ala Ala Ser Ser Thr Pro Asn Thr Val Thr Met			
	275	280	285	
35	Glu Met Gln Cys Pro Ser Gly Asn Ala Ser			
	290	295		
	(2) INFORMATION FOR SEQ ID NO:77:			
	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 299 amino acids			
40	(B) TYPE: amino acid			
	(C) STRANDEDNESS: single			
	(D) TOPOLOGY: linear			
	(ii) MOLECULE TYPE: peptide			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:			
45	Thr Thr Glu Ala Val Leu Asn Thr Phe Ile Ile Phe Val Gly Gly Pro			
	1	5	10	15
	Ala Ile Val Leu Ile Thr Gln Leu Leu Thr Asn Arg Val Leu Gly Tyr			

- 132 -

	20	25	30	
	Ser Thr Pro Thr Ile Tyr Met Arg Asn Leu Tyr Ser Thr Asn Phe Leu			
	35	40	45	
5	Thr Leu Thr Val Leu Pro Phe Ile Val Leu Ser Asn Gln Trp Leu Leu			
	50	55	60	
	Pro Ala Cys Tyr Val Ala Ser Cys Lys Phe Leu Ser Val Ile Tyr Tyr			
	65	70	75	80
	Ser Ser Cys Thr Val Gly Phe Ala Thr Val Ala Leu Ile Ala Ala Asp			
	85	90	95	
10	Arg Tyr Arg Val Leu His Lys Arg Thr Tyr Ala Arg Gln Ser Tyr Arg			
	100	105	110	
	Ser Leu Leu Leu Thr Trp Leu Ala Gly Leu Ile Phe Ser Val Pro Ala			
	115	120	125	
15	Ala Val Tyr Thr Thr Val Val Met His His Asp Ala Asn Asp Thr Asn			
	130	135	140	
	Asn Thr Asn Gly His Ala Thr Cys Val Leu Tyr Phe Val Ala Glu Glu			
	145	150	155	160
	Val His Thr Val Leu Leu Ser Trp Lys Val Leu Leu Thr Met Val Trp			
	165	170	175	
20	Gly Ala Ala Pro Val Ile Leu Phe Tyr Ala Phe Phe Tyr Ser Thr Val			
	180	185	190	
	Gln Arg Thr Ser Gln Lys Gln Arg Ser Arg Thr Leu Thr Phe Val Ser			
	195	200	205	
25	Val Leu Leu Ile Ser Phe Val Ala Leu Gln Thr Pro Tyr Val Ser Leu			
	210	215	220	
	Met Ile Phe Asn Ser Tyr Ala Thr Thr Ala Trp Pro Met Cys Glu His			
	225	230	235	240
	Leu Thr Leu Arg Arg Thr Ile Gly Thr Leu Ala Arg Val Val Pro His			
	245	250	255	
30	Leu His Cys Leu Ile Asn Pro Ile Leu Tyr Ala Leu Leu Cys His Asp			
	260	265	270	
	Phe Leu Gln Arg Met Arg Gln Cys Phe Arg Gly Gln Leu Ile Asp Arg			
	275	280	285	
35	Ala Phe Leu Arg Ser Gln Gln Asn Gln Arg Ala			
	290	295		
	(2) INFORMATION FOR SEQ ID NO:78:			
	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 283 amino acids			
	(B) TYPE: amino acid			
40	(C) STRANDEDNESS: single			
	(D) TOPOLOGY: linear			
	(ii) MOLECULE TYPE: peptide			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:			
45	Leu Gly Val Trp Leu Met Ile Val Gly Thr Phe Leu Leu Val Ile Thr			
	1	5	10	15
	Thr Ile Leu Tyr Tyr Arg Arg Lys Lys Lys Ser Pro Ser Asn Thr Tyr			
	20	25	30	

- 133 -

	Ile Cys Asn Leu Ala Val Ala Asp Leu Leu Ile Val Val Gly Leu Pro
	35 40 45
	Phe Phe Leu Glu Tyr Ala Lys His His Pro Lys Leu Ser Arg Glu Val
	50 55 60
5	Val Cys Ser Gly Leu Asn Ala Cys Phe Tyr Ile Cys Leu Phe Ala Gly
	65 70 75 80
	Val Cys Phe Leu Ile Asn Leu Ser Met Asp Arg Tyr Cys Val Ile Val
	85 90 95
10	Trp Gly Val Glu Leu Asn Arg Val Arg Asn Asn Lys Arg Ala Thr Cys
	100 105 110
	Trp Val Val Ile Phe Trp Ile Ile Ala Val Leu Met Gly Met Pro His
	115 120 125
	Tyr Ile Met Tyr Ser His Thr Asn Asn Glu Cys Val Gly Trp Phe Ala
	130 135 140
15	Asn Glu Thr Ser Cys Trp Phe Pro Val Phe Leu Asn Thr Ly Val Asn
	145 150 155 160
	Ile Cys Gly Tyr Leu Ala Pro Ile Ala Leu Met Ala Tyr Tyr Asn Arg
	165 170 175
20	Met Val Arg Phe Ile Ile Asn Tyr Val Gly Lys Trp Phe Met Gln Thr
	180 185 190
	Leu His Val Leu Leu Val Val Val Val Ser Phe Ala Ser Phe Trp Phe
	195 200 205
	Pro Phe Asn Leu Ala Leu Phe Leu Glu Ser Ile Arg Leu Ile Ala Gly
	210 215 220
25	Val Tyr Asn Asp Thr Leu Gln Asn Val Ile Ile Phe Cys Leu Tyr Val
	225 230 235 240
	Gly Gln Phe Ile Ala Tyr Val Arg Ala Cys Leu Asn Pro Gly Ile Tyr
	245 250 255
30	Ile Leu Val Cys Thr Trp Phe Leu Arg Val Phe Ala Cys Cys Cys Val
	260 265 270
	Lys Gln Glu Ile Pro Tyr Gln Asp Ile Asp Ile
	275 280
	(2) INFORMATION FOR SEQ ID NO:79:
	(i) SEQUENCE CHARACTERISTICS:
35	(A) LENGTH: 295 amino acids
	(B) TYPE: amino acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear
	(ii) MOLECULE TYPE: peptide
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:
	Pro Val Thr Leu Phe Leu Tyr Gly Val Val Phe Leu Phe Gly Ser Ile
	1 5 10 15
	Gly Asn Phe Leu Val Ile Phe Thr Ile Thr Trp Arg Arg Arg Ile Gln
	20 25 30
45	Cys Ser Gly Asp Val Tyr Phe Ile Asn Leu Ala Ala Ala Asp Leu Leu
	35 40 45
	Phe Val Cys Thr Leu Pro Leu Trp Met Gln Tyr Leu Leu Asp His Asn

- 134 -

	50	55	60	
	Ser Leu Ala Ser Leu Ile Pro Cys Thr Leu Leu Thr Ala Cys Phe Tyr			
65	65	70	75	80
5	Val Ala Ile Thr Ala Ser Leu Cys Phe Ile Thr Glu Ile Ala Leu Ile			
	85		90	95
	Asp Arg Tyr Tyr Ala Ile Val Tyr Met Arg Tyr Arg Pro Val Lys Ile			
	100	105		110
	Gln Ala Cys Leu Phe Ser Ile Phe Trp Trp Ile Phe Ala Val Ile Ile			
	115	120		125
10	Ala Ile Pro His Phe Met Val Val Ile Thr Lys Lys Asp Asn Gln Cys			
	130	135		140
	Met Thr Asp Tyr Asp Tyr Leu Glu Val Ser Tyr Pro Ile Ile Leu Asn			
	145	150	155	160
15	Val Glu Leu Met Leu Gly Ala Phe Val Ile Pro Leu Ser Val Ile Ser			
	165		170	175
	Tyr Cys Tyr Tyr Arg Ile Ser Arg Ile Val Ala Val Ser Gln Ser Arg			
	180	185		190
	His Lys Gly Arg Ile Val Arg Val Leu Ile Ala Trp Leu Val Phe Ile			
	195	200		205
20	Ile Phe Trp Leu Pro Tyr His Leu Thr Leu Phe Val Asp Thr Ile Ile			
	210	215		220
	Lys Leu Leu Lys Trp Ile Ser Ser Ser Cys Glu Phe Glu Arg Ser Leu			
	225	230	235	240
25	Lys Arg Ala Leu Ile Leu Thr Glu Ser Leu Ala Phe Cys His Cys Cys			
	245		250	255
	Leu Asn Pro Leu Leu Tyr Val Phe Val Ile Gly Thr Lys Phe Arg Lys			
	260	265		270
	Asn Tyr Thr Val Cys Trp Pro Ser Phe Ala Ser Asp Ser Phe Pro Ala			
	275	280		285
30	Met Tyr Pro Gly Thr Arg Ala			
	290	295		
	(2) INFORMATION FOR SEQ ID NO:80:			
	(i) SEQUENCE CHARACTERISTICS:			
35	(A) LENGTH: 31 amino acids			
	(B) TYPE: amino acid			
	(C) STRANDEDNESS: single			
	(D) TOPOLOGY: linear			
	(ii) MOLECULE TYPE: peptide			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:			
40	Asp Asp Asp Asp Asn Ile Trp Ser Ile Phe Asp Trp Ile Gly Tyr Leu			
	1	5	10	15
	Asn Ser Ile Ser Met Val Ile Tyr Thr Leu Phe Lys Lys Lys Lys			
	20	25		30
	(2) INFORMATION FOR SEQ ID NO:81:			
45	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 34 amino acids			
	(B) TYPE: amino acid			
	(C) STRANDEDNESS: single			

- 135 -

(D) TOPOLOGY: linear  
 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:  
 Asp Asp Asp Asp Asn Ile Trp Asn Ile Phe Ser Thr Ile Gly Tyr Leu  
 5 1 5 10 15  
 Asn Ser Ile Ser Pro Val Ser Val Ile Met His Ile Tyr Gly Lys Lys  
 20 25 30  
 Lys Lys

10 (2) INFORMATION FOR SEQ ID NO:82:  
 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 29 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 15 (D) TOPOLOGY: linear  
 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:  
 Asp Asp Asp Asp Gly Tyr Ser Ile Tyr Asp Thr Leu Val Thr Phe Ala  
 1 5 10 15  
 Ile Asn Pro Val Tyr Ile Thr Val Phe Lys Lys Lys Lys  
 20 25

(2) INFORMATION FOR SEQ ID NO:83:  
 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 31 amino acids  
 25 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear  
 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:  
 Asp Asp Asp Asp Asn Ala Trp Ser Ala Phe Asp Trp Ala Leu Tyr Leu  
 30 1 5 10 15  
 Asn Ser Ile Ser Met Ala Ile Tyr Thr Tyr Ala Lys Lys Lys  
 20 25 30

(2) INFORMATION FOR SEQ ID NO:84:  
 35 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 23 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear  
 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:  
 Leu Phe Ser Phe Ile Thr Trp Leu Gly Tyr Ala Asn Ser Ser Leu Asn  
 40 1 5 10 15  
 Pro Ile Ile Tyr Thr Thr Phe  
 45 20

(2) INFORMATION FOR SEQ ID NO:85:  
 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 23 amino acids  
 (B) TYPE: amino acid  
 50 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear  
 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:  
 Tyr Thr Ile Tyr Ser Ser Ser Val Val Phe Phe Ala Pro Ser Leu Ala  
 55 1 5 10 15  
 Ile Met Val Ile Thr Tyr Thr  
 20

- 136 -

## (2) INFORMATION FOR SEQ ID NO:86:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 22 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Ile Trp Leu Thr Ser Asp Ile Met Ser Thr Ser Ser Ile Leu His Asn  
 10 1 5 10 15

Leu Cys Val Ile Ser Phe  
 20

## (2) INFORMATION FOR SEQ ID NO:87:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 30 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Ile Trp Ser Ile Phe Ser Ser Asp Ile Val Val Gly Tyr Ala Asn His  
 20 1 5 10 15

Ser Ser Leu Ala Ile Met Cys Pro Ile Val Ile Tyr Thr Val  
 20 25 30

## 25 (2) INFORMATION FOR SEQ ID NO:88:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 29 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Ile Phe Thr Ile Phe Ser Ser Asp Ile Ala Val Gly Tyr Ala Asn His  
 1 5 10 15

35 Ser Ser Ala Ala Ile Met Pro Ile Val Ile Tyr Ser Val  
 20 25

## (2) INFORMATION FOR SEQ ID NO:89:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 24 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

40 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

Lys Asn Ala Ser Ala Leu Leu Ser Val Ile Ile Ile Asn Ser Ile Gly  
 45 1 5 10 15

Gly Asn Val Val Thr Ala Val Ser  
 20

## 50 (2) INFORMATION FOR SEQ ID NO:90:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 22 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

55 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Tyr Phe Leu Met Ser Leu Ala Val Thr Asp Leu Val Val Ser Phe Val  
 1 5 10 15

- 137 -

Met Pro Val Ser Ala Leu  
20

## (2) INFORMATION FOR SEQ ID NO:91:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 23 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Ala Ile Thr Lys Ile Ala Ile Thr Trp Ala Ile Ser Gly Val Ser Val  
1 5 10 15

Pro Phe Ile Pro Val Trp Gly  
20

## 15 (2) INFORMATION FOR SEQ ID NO:92:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 24 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Leu Gly Ile Ile Phe Gly Thr Phe Ile Ile Ile Trp Leu Pro Phe Phe  
1 5 10 15

25 Ile Thr Asn Leu Val Ser Pro Ile  
20

## (2) INFORMATION FOR SEQ ID NO:93:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 23 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

30 Ile Trp Ile Ser Leu Asp Val Leu Phe Ser Thr Ala Ser Ser Ile Met  
1 5 10 15

His Leu Cys Ala Ile Ser Leu  
20

## 40 (2) INFORMATION FOR SEQ ID NO:94:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 23 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

45 Gly Tyr Thr Ile Tyr Ser Thr Leu Val Thr Phe Tyr Ile Pro Ser Val  
1 5 10 15

50 Ile Met Val Ile Thr Tyr Gly  
20

## (2) INFORMATION FOR SEQ ID NO:95:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 23 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

- 138 -

Leu Leu Asn Phe Phe Asn Trp Ile Gly Tyr Leu Asn Ser Leu Ile Asn  
1 5 10 15

Pro Val Ile Tyr Thr Leu Phe  
20

- 141 -

22. The method of claim 21, wherein said psychotic disorder is a schizophrenia.

23. The method of claim 20, wherein said composition is administered to provide said polypeptide, fragment or consensus peptide thereof, in an amount ranging from about 0.01 µg to 100 mg/kg per day.

24. The method of claim 23, wherein said composition is administered to provide said polypeptide, fragment or consensus peptide thereof, in an amount ranging from about 10µg to 10 mg/kg per day.

25. The method of claim 20, wherein said administering is by oral, mucosal, intravenous, intramuscular or parenteral administration.

26. A method for producing a polypeptide according to claim 1, wherein said polypeptide is a recombinant polypeptide obtained from a recombinant host which expresses a heterologous nucleic acid encoding said polypeptide, comprising the steps of:

20 (A) providing a host comprising a recombinant nucleic acid encoding a polypeptide according to claim 1 in expressible form;

(B) culturing said host under conditions such that said polypeptide is expressed in recoverable amounts; and

(C) recovering said polypeptide produced by said host.

27. The method of claim 26, further comprising:

(D) purifying said polypeptide.

28. The method of claim 26, wherein said host is a bacteria or a eukaryotic cell.

29. The method of claim 28, wherein said eukaryotic cell is a mammalian cell, an insect cell or a yeast cell.

30. A method for producing a polypeptide according to claim 1, comprising:

(A) chemically synthesizing a polypeptide according to claim 1 in recoverable amounts; and

35 (B) recovering said polypeptide.

- 142 -

31. A method for isolating a G-protein coupled receptor, fragment or consensus sequence thereof, or a protein that binds the G-protein coupled receptor, comprising

5 (A) providing a bound support, said support being bound to a polypeptide according to claim 1, or an antibody, anti-idiotype antibody, or a fragment thereof;

10 (B) contacting a sample containing said G-protein coupled receptor or said protein that binds a G-protein coupled receptor to said bound support, such that said receptor or protein is reversibly bound to said bound support; and

15 (C) recovering said receptor or protein that is attached to the bound support by dissociating the receptor or protein under conditions that cause elution or dissociation of the receptor or protein from said bound support.

32. A method according to claim 31, wherein said GPR is a dopamine receptor.

33. An antibody, anti-idiotype antibody or a fragment of said antibody or anti-idiotype antibody, that specifically displays an epitope of a G-protein coupled receptor polypeptide, according to claim 1.

34. A recombinant nucleic acid comprising a nucleotide sequence encoding a G-protein coupled receptor polypeptide according to claim 1.

35. A vector comprising a nucleic acid according to claim 34.

36. A host cell comprising the nucleic acid of claim 34.

37. A host cell according to claim 36, wherein said host cell is selected from a mammalian cell, a yeast cell, a bird cell or an insect cell.

38. A host cell according to claim 36, wherein, when said nucleic acid is expressed as said receptor polypeptide in said host cell, a receptor binding molecule comprising said env binding domain binds to said receptor polypeptide.

WHAT IS CLAIMED IS:

1. A G-protein coupled receptor polypeptide, consisting essentially of an amino acid sequence of 15 to 40 amino acids substantially corresponding to a fragment or consensus peptide of a transmembrane domain of a G-protein coupled receptor, wherein said polypeptide has a GPR-related biological activity selected from binding a GPR ligand or modulating GPR ligand binding to a GPR.

2. A polypeptide according to claim 1, wherein said polypeptide is selected from a synthetic polypeptide, a recombinant polypeptide or a purified polypeptide.

3. A polypeptide according to claim 1, wherein said G-protein coupled receptor is a receptor selected from a cAMP receptor, an adenosine receptor, a  $\beta$ -adrenergic receptor, a muscarinic acetylcholine receptor, an  $\alpha$ -adrenergic receptor, a serotonin receptor, a histamine H<sub>2</sub> receptor, a thrombin receptor, a kinin receptor, a follicle stimulating hormone receptor, an opsin, a rhodopsin, an odorant receptor, a cytomegalovirus receptor, or a mas oncogene GPR.

4. A polypeptide according to claim 1, wherein said transmembrane domain is selected from at least one of transmembrane domain TM1, TM2, TM3, TM4, TM5, TM6 or TM7.

5. A polypeptide according to claim 3, wherein said transmembrane domain is a D<sub>2</sub> receptor transmembrane segment III or segment V.

6. A polypeptide according to claim 4, wherein said polypeptide has the amino acid sequence of Fig. 2 (SEQ ID NO:2).

7. A polypeptide according to claim 4, wherein said polypeptide has the amino acid sequence of Fig. 3 (SEQ ID NO:3).

8. A polypeptide according to claim 4, wherein said polypeptide has an amino acid sequence selected from one of SEQ ID NOS:80-95.

9. A polypeptide according to claim 4, wherein said polypeptide has an amino acid sequence of one of SEQ ID NOS:96-348.

10. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:96-225.

- 140 -

11. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:226-289.

5 12. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:290-297.

13. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:298-324.

10 14. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:325-338.

15 15. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:339-348.

16. A polypeptide according to claim 3, wherein said transmembrane domain is a dopamine receptor transmembrane domain selected from the group consisting of a D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub> or D<sub>5</sub> transmembrane domain.

20 17. A composition comprising a polypeptide according to claim 1, or a pharmaceutically acceptable ester, ether, sulfate, carbonate, glucuronide or salt thereof, and a pharmaceutically acceptable carrier.

25 18. A composition according to claim 16, wherein said transmembrane domain is D<sub>2</sub> receptor transmembrane segment III or segment V.

30 19. A composition according to claim 18, further comprising a drug selected from a phenothiazine derivative, a thioxanthine derivative, a butyrophenone derivative, a dihydroindolone, a dibenzoxazepine derivative and an atypical neuroleptic.

35 20. A method for treating a subject suffering from a pathology related to an abnormality of a G-protein coupled receptor, comprising administering to said subject a therapeutically effective amount of composition according to claim 16.

21. The method of claim 20, wherein said pathology is a psychotic disorder.

- 143 -

39. A host cell according to claim 37, wherein said host cell is a mammalian cell selected from a human cell, a primate cell or a rodent cell.

40. A method for isolating a protein that binds a  
5 G-protein coupled receptor, comprising

(A) providing a bound support, said support being bound to a polypeptide according to claim 1, or anti-idiotype antibody thereto;

10 (B) contacting a sample containing said protein that binds a G-protein coupled receptor to said bound support, such that said protein is reversibly bound to said bound support; and

15 (C) recovering said protein that is attached to the bound support by dissociating the receptor or protein under conditions that cause elution or dissociation of the protein from said bound support.

41. A method according to claim 40, wherein said GPR is a dopamine receptor.

1/14

LSLLSLLSLLLSSLSSLLSLYYY

FIGURE 1

WO 94/05695

PCT/US93/08528

2/14



DDIFVTLDVLFSTASILNL~~SAISL~~KKK

FIGURE 2

3/14

DYAI**F**VLYASA**W**LSFNC**P**FIVTLNIK

DEC 4 1994

FIGURE 3

4/14

KAVVYSSIVSFYVFID

FIGURE 4

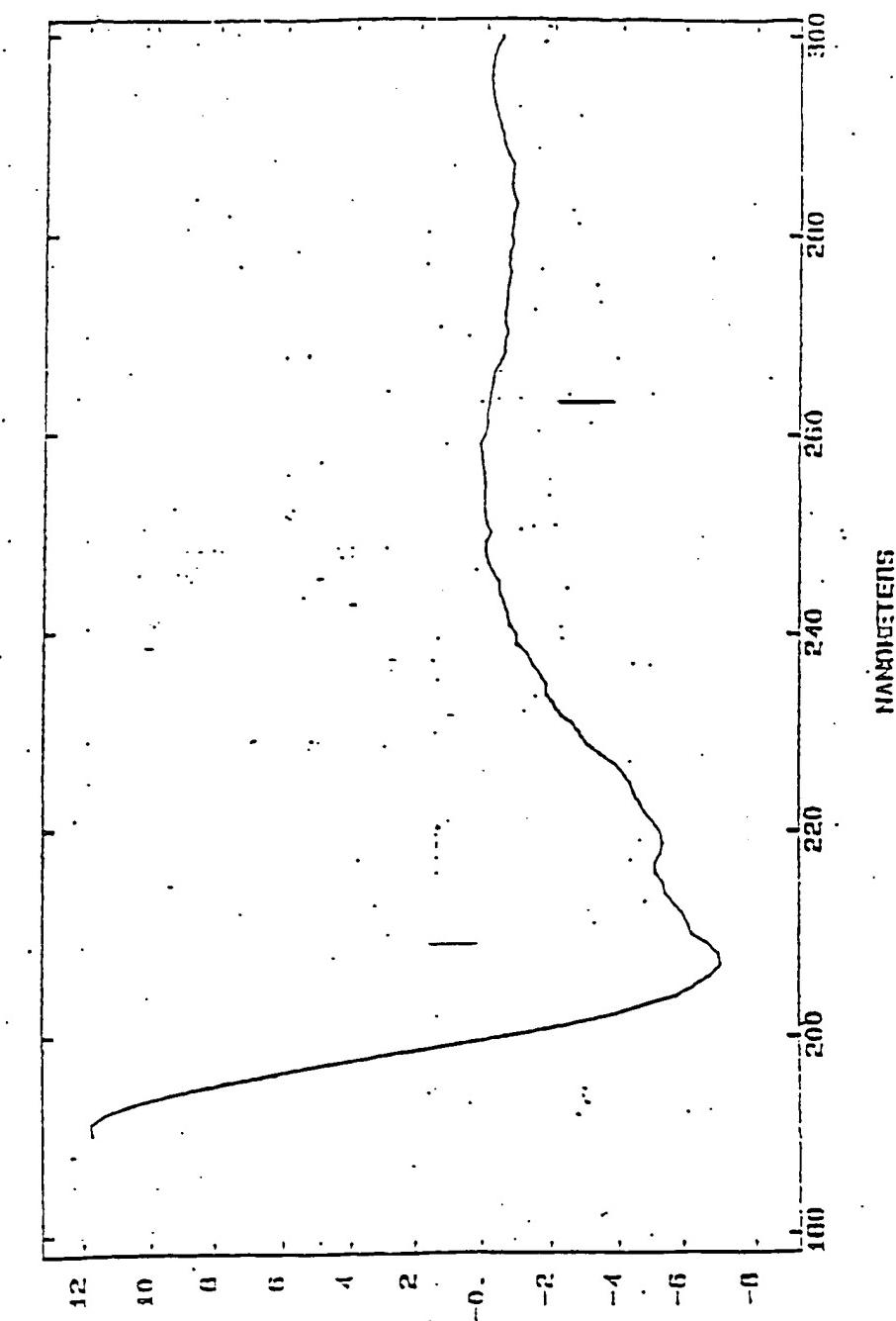
---

5/14

DCDVVFVFDIMLCTASIFNLCAISVGK

FIGURE 5

6/14



conc7a

MNMGETENS

Fig. 6

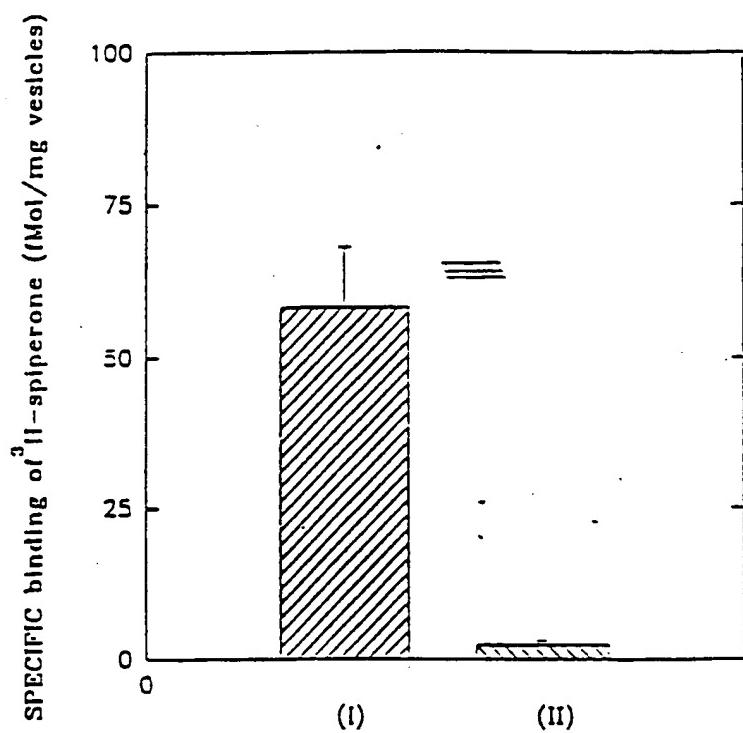


FIGURE 7

1. Dictyostelium cAMP receptor (Klein et al., 1988)
2. Dog adenosine A2 receptor (RDC3) (Libert et al., 1989b)
3. Dog adenosine A1 receptor (RDC7) (Libert et al., 1989b)
4. Human α1 muscarinic acetylcholine receptor (Peralta et al., 1987)
5. Human α2 muscarinic acetylcholine receptor (Peralta et al., 1987)
6. Human α3 muscarinic acetylcholine receptor (Peralta et al., 1987)
7. Human α4 muscarinic acetylcholine receptor (Peralta et al., 1988)
8. Human α5 muscarinic acetylcholine receptor (Bonner et al., 1988)
9. Human beta 1 adrenergic receptor (Frigola et al., 1987)
10. Human beta 2 adrenergic receptor (Nobilia et al., 1987a)
11. Human beta 3 adrenergic receptor (Lemarie et al., 1989)
12. Cow alpha 1 adrenergic receptor (Schwinn et al., 1990)
13. Rat alpha 1B adrenergic receptor (Valeg., et al., 1990)
14. Human alpha 2 C1 adrenergic receptor (McLean et al., 1988)
15. Human alpha 2 C2 adrenergic receptor (Lomasney et al., 1990)
16. Human alpha 2 C10 adrenergic receptor (Nobilia et al., 1987c)
17. Rat alpha 2 adrenergic receptor R20 (Lander et al., 1991)
18. Drosophila octopamine receptor (Barry et al., 1990)
19. Human dopamine D1 receptor (Barry et al., 1990)
20. Human dopamine D3 receptor (Sunahara et al., 1991)
21. Human dopamine D2 receptor (Grandy et al., 1989)
22. Human dopamine D4 receptor (Girao et al., 1990)
23. Human serotonin 1d receptor [RDC4] (Roeblin and Mocalf, 1991)
24. Human serotonin 1a receptor (Nobilia et al., 1987b)
25. Rat serotonin 1c receptor (Julius et al., 1988)
26. Rat serotonin 1e receptor (Julius et al., 1990)
27. Rat serotonin 2 receptor (Julius et al., 1990)
28. Human histamine H2 receptor (Ganz et al., 1991)
29. Human N-formyl peptide receptor (Boulouy et al., 1990)
30. Human C5a anaphylatoxin receptor (Gerard and Gerard, 1991)
31. Human cholinin receptor (Vu et al., 1991)
32. Human cholinesterase A2 receptor (Mizra et al., 1991)
33. Human IL-8 receptor (Murphy and Tiffay, 1991)
34. Guinea-pig platelet-activating factor receptor (Honda et al., 1991)
35. Cow endothelin 1 receptor (Arai et al., 1990)
36. Rat non-isopeptidoleucotrienoic endothelin receptor (Sakurai et al., 1990)
37. Mouse bombazine/gastrin releasing peptide receptor (Spindel et al., 1991)
38. Rat neuropeptide B preferring bombazine receptor (Moto et al., 1991)
39. Human vasoactive intestinal peptide (Broocharas et al., 1991)
40. Rat sourcetain receptor (Franke et al., 1990)
41. Rat bradykinin receptor (Metzger et al., 1991)
42. Mouse thyrotropin-releasing hormone receptor (Straub et al., 1990)
43. Human neuropeptide A (NP) receptor (Gerard et al., 1990)
44. Rat substance P receptor (Tokuda et al., 1989)
45. Rat neuropeptide K receptor (Saligmento et al., 1990)
46. Bovine adrenomedullin II type-1 receptor (Kosaki et al., 1991)
47. Human vas deferens (angiotensin) receptor (Young et al., 1986)
48. Human luteinizing-hormone receptor (Frasier et al., 1990)
49. Human thyrotropin receptor (Elbert et al., 1989a)
50. Human follitropin stimulating hormone receptor (Minagish et al., 1991)
51. Human rhodopsin (Nathans and Deegan, 1984)
52. Human green opsin (Nathans et al., 1986)
53. Human rod opsin (Nathans et al., 1986)
54. Human blue opsin (Nathans et al., 1986)
55. Olfact receptor F3 (Buck and Axel, 1991)
56. Olfact receptor F3 (Buck and Axel, 1991)
57. Olfact receptor F6 (Buck and Axel, 1991)
58. Olfact receptor F12 (Buck and Axel, 1991)
59. Olfact receptor I3 (Buck and Axel, 1991)
60. Olfact receptor I7 (Buck and Axel, 1991)
61. Olfact receptor I8 (Buck and Axel, 1991)
62. Olfact receptor I9 (Buck and Axel, 1991)
63. Olfact receptor I14 (Buck and Axel, 1991)
64. Olfact receptor I15 (Buck and Axel, 1991)
65. Human cannabinoid receptor (Matuda et al., 1990)
66. Mouse Glucocorticoid-induced receptor (Marrigan et al., 1991)
67. Rat PCIR (Eva et al., 1990)
68. Human endothelial cell GPR 01a and Maciag, 1990
69. Rat taste G-protein coupled receptor 1 (Meyerhof et al., 1991a)
70. Rat RGR7 (Meyerhof, DNA and Cell Biology, In press, 1991b).
71. Human fibroblast GPR (Reiss et al., 1990)
72. Cycomegalovirus Human GPR, US33 (Choo et al., 1990)
73. Cycomegalovirus (Human) GPR, US27 (Choo et al., 1990)
74. Cycomegalovirus (Human) GPR, US28 (Choo et al., 1990)

FIGURE 8A

### FIGURE 8B

1

1	SLVLLFADFSSPLCIVAVI	CYRLLCANNVTA	-YIACCATSTFDQFPSTIITL	IVAVNCGCPVYTA
2	YVTVLAALVLAIIQVWVCAV-	IVSILQWVTH	-TFWSLAAADIAVCGVAPPFAT	ISTPFOAHCNA
3	AYISGIVLAL/SVPGVVLIVWAV-	KVNCALCAT	-CTIVSLAVAVGAVAVGIVPLAII	INICPICTNT
4	VAFTEVLSLSATVTCIVLVIAT-	KVNLCEVAN	-TFLSLACDGLITGTSMPCTT	YIAGCH-HAELIA
5	WTIVVAGSLSLTTCIVLVIAT-	KVNLCEVAN	-TFLSLACDGLITGTSMPCTT	YIDMR-HAELIA
6	WTFATCIVLALVTTGIVLTVVS-	KVNLCEVAN	-TFLSLACDGLITGTSMPCTT	YINGC-PZLAW
7	MVTLATVLSLSLTWVGNLIVLVI-	KVNLCEVAN	-TFLSLACDGLITGTSMPCTT	YIAGCH-HAELIA
8	VITSLAWTAWSLMIVCIVLVCSP-	KVNLCEVAN	-TFLSLACDGLITGTSMPCTT	YIAGCH-HAELIA
9	SAGCIVALVIVLIVGIVMIVVIAA	ICPA-LTEN	-TFWSLAAADIAVCGVAPPFAT	LYWDR-WEYCSFT
10	WQGIVMSLVIVAVGIVMIVVIAA	ICPA-LTEN	-TFLSLACDGLITGTSMPCTT	KJLMOH-WITGTY
11	AIALGALLALAVATVCGIVLVALA	ICPA-LTEN	-TFWSLAAADIAVCGVAPPFAT	LACRSH-APLATO
12	AIISGIVLAL/SVPGVVLIVWAV-	ICRLLKSVTH	-TIVMLAVADLITLITLTFPSAI	FELEY-HAFGAT
13	ASVGEVLSLIVLIVGIVLIVLVA-	ICRLLKSVTH	-TIVMLAVADLITLITLTFPSAI	LEVLSI-WLCSR
14	VACLAIVGIVLIVTIVGIVLIV-	ICRLLKSVTH	-TFLWSLAAADIAVCGVAPPFAT	NEUPAY-WTCGV
15	DAALAAITLIVLITLIVGIVLIV-	ICRLLKSVTH	-TFLWSLAAADIAVCGVAPPFAT	NEULCY-WTART
16	TEVACAGLIVLIVLIVGIVLIV-	ICRLLKSVTH	-TFLWSLAAADIAVCGVAPPFAT	NEVNEY-WTCKT
17	TIVELAGLIVLIVLIVGIVLIV-	ICRLLKSVTH	-TFLWSLAAADIAVCGVAPPFAT	NEVNEY-WTCKT
18	LEALIVLIVLIVLIVGIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	TSILOR-WEFCXL
19	RILACTLSLIVLIVLIVGIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	AEZAGT-WPFEST
20	QVTAACLIVLIVLIVLIVGIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	AEVAGT-WPFEST
21	TFVTAACLIVLIVLIVLIVGIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	LEWGE-WTRSRK
22	-ATPALSTCLLAVLIVFGRIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	LEVTECANTSRIC
23	QWALVCGVLLIVGIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	SEVOQAHILSPRL
24	KEISLAVLIVLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	YVCLNK-WTLCV
25	VISLILGTC-AVLQAVWVIAA	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	ZLTDYVWLPRTI
26	QWPAFLSTWVIMTCGIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	YIICYRULPSIC
27	QWMLALIVLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	YOLSOX-WHSTXV
28	-ITIVMLAVLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
29	-ITIVMLAVLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
30	DILALVIFAWLIVLIVGIVLIVWV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
31	TFVPSVITGIVLIVLIVLIVWV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
32	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
33	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
34	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
35	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
36	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
37	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
38	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
39	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
40	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
41	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
42	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
43	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
44	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
45	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
46	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
47	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
48	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
49	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
50	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
51	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
52	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
53	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
54	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
55	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
56	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
57	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
58	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
59	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
60	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
61	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
62	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
63	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
64	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
65	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
66	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
67	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
68	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
69	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
70	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
71	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
72	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
73	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	
74	-TIVMLAVADLIVLIVLIVLIV-	ICRLLKSVTH	-TIVMLAVADLIVLIVLIVFMA	

FIGURE 8C

11/14

3

4

1	2	3	4
1	PCGGSAGAATLHESSTY UTAGTCGGTSSSTFATL WAAVIVGSSSTPDDGAV	DRYALVTPDNGVPRR CRAVVAECPVPPVPRR	ANGIISAVAVLSFACLTPLG CAVAAACCCPSTVNCVPLG
2			OTV/CVGY WNSOPRECVSS WRLZAGRADANGSSECVG
3			
4	DHALSYVASVASVLYLISST	DRYFSTPPLSTRANG-PRR	-HALMIGCLAVLSTV-LAPALIFV
5	DHALSYVASVASVLYLISST	DRYFSTPPLSTRANG-TKA	-AGPHCAAANVLSL-LAPALIFV
6	DHALSYVASVASVLYLISST	DRYFSTPPLSTRANG-TKA	-AGPHCAAANVLSL-LAPALIFV
7	DHALSYVASVASVLYLISST	DRYFSTPPLSTRANG-TKA	-ACIDCAAANVLSV-LAPALIFV
8	DHALSYVASVASVLYLISST	DRYFSTPPLSTRANG-PKA	-ACIDCAAANVLSV-LAPALIFV
9	DTASVQVLTCTASIEELAL	DRYLAATSPPFROSLL-PRR	-ARLVCVTHAISALVSLPLDMM
10	FATISDVQVLTCTASIEELAL	DRYLAATSPPFROSLL-PRR	-ARTVLSVAVTVSCSPLTQMM
11	DTASVQVLTCTASIEELAL	DRYLAATPPLCALVTRC	-ARTAVLWVAVVSAVSVAPLGV
12	IVQAVVQLCTASIEELAL	DRYLGSTPLCPTTVCRR	-CIALLCHMHSLSVTSICPLF-GV
13	IVQAVVQLCTASIEELAL	DRYLGSTPLCPTTVCRR	-AIIALLSVWVLSVTSICPLF-GV
14	VPAALVLTCTSSVNLCAISL	DRYSVTCAVEENLCPKPR	-WATVAVMVLISAVESFPPPLVSL
15	VPAALVLTCTSSVNLCAISL	DRYAVASALEENSKCPKPR	-INCIIZTMLIAVVISLPPPLVSL
16	VPAALVLTCTSSVNLCAISL	DRYAVASALEENSKCPKPR	-IAIIITWVAVISAVISFPPPLISI
17	VPAALVLTCTSSVNLCAISL	DRYAVASALEENSKCPKPR	-IAIIITWVAVISAVISFPPPLISI
18	VPAALVLTCTSSVNLCAISL	DRYAVASALEENSKCPKPR	-IAIIITWVAVISAVISFPPPLISI
19	IVPAALVLTCTSSVNLCAISL	DRYAVASISPFVKCIPR-KA	-VILLSVTSLILSISSPPLF-GV
20	IVPAALVLTCTSSVNLCAISL	DRYAVASISPFVKCIPR-KA	-AFPLISVANTLVSLESTPVQLSV
21	IVPAALVLTCTSSVNLCAISL	DRYAVASISPFVKCIPR-KA	-ALVHVGAVLTSLSLSTIPVQLSV
22	IVPAALVLTCTSSVNLCAISL	DRYAVAVPPLV-DESSKRR	-WVMSVAVVLSVLSVSC-PLFGL
23	IVPAALVLTCTSSVNLCAISL	DRYAVAVPPLV-DESSKRR	-WVMSVAVVLSVLSVSC-PLFGL
24	IVPAALVLTCTSSVNLCAISL	DRYAVAVVPLV-DESSKRR	-OILLCATVLLSAVAA-PVLC
25	IVPAALVLTCTSSVNLCAISL	DRYAVAVVPLV-DESSKRR	-OILLCATVLLSAVAA-PVLC
26	IVPAALVLTCTSSVNLCAISL	DRYAVAVVPLV-DESSKRR	-OILLCATVLLSAVAA-PVLC
27	IVPAALVLTCTSSVNLCAISL	DRYAVAVVPLV-DESSKRR	-OILLCATVLLSAVAA-PVLC
28	IVPAALVLTCTSSVNLCAISL	DRYAVAVVPLV-DESSKRR	-OILLCATVLLSAVAA-PVLC
29	FJFTVODINLFGSVFLALIAL	DRGCVLUPVTCMRCVSLAK-	-XVIGVPMALL-TLPVII-
30	HJFJLQVNLCAISLHATSA	DRGFLVTTKPTWCNTVRC	-WTDCAVAVLALL-TIPSFL-
31	FJFJLQVNLCAISLHATSA	DRGFLLVPHCSLSRRLGA	-ASTVCAVAVLALL-TIPSFL-
32	FJFJLQVNLCAISLHATSA	DRGFLVTPRSPVAVSRR	-ASTVCAVAVLALL-TIPSFL-
33	FJFJLQVNLCAISLHATSA	DRGFLVWACRLTCKRIVK-	-TICSTCATSLL-ALPVLI
34	FJFJLQVNLCAISLHATSA	DRGFLVWACRLTCKRIVK-	-TICSTCATSLL-ALPVLI
35	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-DILVSVNLLSLL-AIPFAIGT
36	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
37	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
38	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
39	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
40	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
41	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
42	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
43	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
44	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
45	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
46	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
47	FJFJLQVNLCAISLHATSA	DRGFLVWAVRVOGCGPLV	-WVMSVAVVLSVLSVSC-PLFGL
48	IGGTIVLASLVSITVIT	DRMHTTAHKDKRURK	-NLLIMGSLVLSLNLHPLVGS
49	IGGTIVLASLVSITVIT	DRMHTTAHKDKRURK	-ACAVAVGSGCTTLLAVLPGVGS
50	IGGTIVLASLVSITVIT	DRMHTTAHKDKRURK	-ASVVMGCAATAAALSPFGS
51	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
52	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
53	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
54	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
55	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
56	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
57	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
58	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
59	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
60	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
61	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
62	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
63	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
64	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
65	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
66	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
67	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
68	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
69	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
70	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
71	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
72	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
73	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
74	IGGTIVLASLVSITVIT	DRMWCOPQNRVFCR	
75	IGGTIVLASLVSITVIT	DRGFSIHPPLRPLRVRPR	-AVAVGSGCTTLLAVLPGVGS
76	IGGTIVLASLVSITVIT	DRGFSIHPPLRPLRVRPR	-VITVAVTAWPATT-SL2HAIC-
77	IGGTIVLASLVSITVIT	DRGFSIHPPLRPLRVRPR	-ATGCTT/TAVLAVS-SL2HAIC-
78	IGGTIVLASLVSITVIT	DRGFSIHPPLRPLRVRPR	-UFLISACAVISLSS-PLPFTV-
79	IGGTIVLASLVSITVIT	DRGFSIHPPLRPLRVRPR	-UFLISACAVISLSS-PLPFTV-
80	IGGTIVLASLVSITVIT	DRGFSIHPPLRPLRVRPR	-VAVVNLTVWVLSV-PLPFTV-
81	IGGTIVLASLVSITVIT	DRGFSIHPPLRPLRVRPR	-LACAGCALVLLSTV-TSIHOMT-
82	IGGTIVLASLVSITVIT	DRGFSIHPPLRPLRVRPR	-STIHLIITLHAGC-FSVPAAVT-
83	IGGTIVLASLVSITVIT	DRGFSIHPPLRPLRVRPR	-ATCAVIF-4-LAVL-HCPHFTC-
84	IGGTIVLASLVSITVIT	DRGFSIHPPLRPLRVRPR	-CACLSIFWTFAVI-LAIPHMMV

FIGURE 8D

12/14

1	WQHGVSTTYRFG	-LTPFLTWASAVVGET-	SCTYWIKNVSN
2	CCLEVACSTDWPPN	-TAYTTFTWWLPPLLMVLT-	KTFMARRCRKOMESOLPGEKAATLQ
3	KEFKEVISE	-TAYTTFTWWLPPLLMVLT-	EVTTIAROLOXVSASSCPCRTG
4	OCIGFLCP	-LTTGAAAMPVTHVET-	RTYTRTENRAREALOCEPCKGSSSSSTASOPGAESPE?
5	OCIGFLCP	-AVTGTAAAMPVTHVET-	HISLASKRISKICDPTVNCPSVPSLIVGATIVGPNNNMPSSE
6	OCIGFLCP	-AVTGTAAAMPVTHVET-	RTYTRTENRAREALOCEAETLTINTVNTCS3SCESSTELLCO
7	OCIGFLCP	-AVTGTAAAMPVTHVET-	HISLASRSRSMVDDPCTKXXUC-AFLKP?LPGCSVNGPPCGA
8	OCIGFLCP	-AVTGTAAAMPVTHVET-	RTYTRTENRAREALOCESSVYXAEKXOPAHALFASCRCRPT
9	RETROKEDIVNR	AYAASSSWTVPVCHAVVZ-	RTVRENDKVOECSGRATPAPRPPSPSPVPAAPPCTP?
10	NYANETCCITING	PTVLLSSSVSPTVPLVHMTVZ-	RVTCLEAKRCLKXKSERAVENLSVEODGCHCRARSXKTC
11	RCUINPSCAFASH	CTVLLSALSSTVPLTILVPTC	RVWVAATCRLLAEGELXPPESPPAPSRSRSLAPAVGCTAPCZ
12	ICDNEP	FCALFCSSLSPTVPLAVLVC	RTVVAARESPTCASYTKEKSCVTCRCAVCESSCTTA
13	ECVIEP	WTLLASSCITTAPELCHMVA	RTVIVANGVTCXNLAGMDSNSKELJLWHNSKTHLJSTX
14	OCCADET	WTLLASSCITTAPELCHMVA	RTYTRVAREKTCIDORAPGPDGASPTVINGCMAACZAREGTA
15	OCCADE	WTLLASSCITTAPELCHMVA	RTYLCALRNSPCTRAGCPCGCTSGPRDONGCALASACPALAS
16	REINDOK	WTLLASSCITTAPELCHMVA	RTOLANKRCP?SPCPIAVAPPGTTERPNCLESAGCG
17	SKENDOK	WTLLASSCITTAPELCHMVA	RTOLANKRCP?SPCPIAVAPPGTTERPNCLESAGCG
18	PELSTCR	CTVLLSSSCTTIPALMVTYI	LIVVATRRLRERARANLDTALKSTLEPANSSPVMASNSGSX
19	NOSSLSR	TSVLLSSSCTTIPALMVTYI	RTYRRAFRKICRADAALZAVHAUNCG...TPOVECSCPESSTX
20	ICSSLNR	TSVLLSSSCTTIPALMVTYI	RTYLAQVOARISSLEMAEHACSCSSAACAPTSLSRASIX
21	ECIAMP	AWVTTSSVSTVPPFTVTLVVI	KITVLLQURRGNTRNTRSAFRALHAPLCTNPEMLST
22	VGTISNP	DVTTSSVSTVPPFTVTLVVI	RTVWLQURRGNTRNTRSAFRALHAPLCTNPEMLST
23	DCVLDR	DVTTSSVSTVPPFTVTLVVI	ATTGICLORIVVARAALICGURRPSCPSPPTPAPRLPDCG
24	DCWNSQ	STTYSCTCATIPSVLLSILC	RTYRANARBLNPPLTGRU...JLHLTSSASSLESSNSLSHEH
25	ACTISKH	CTVYCTCATIPSVLLSILC	RTFRAAFRIRKVYVQEVGTCATRHEASAPCPKSVNCESSAN
26	TCVLDNP	FVLCGTA-TTPTLIMVTT	LTVLVRATLMLAGCTTIANMSLNFNC...KCGCCEENAPN
27	SCLLADM	FVLCGTA-TTPTLIMVTT	LTXNSLQRA...SLSLDRCAASFSTLPGSSLSLEXLPSRTHR
28	RTKVGVNE	WTGCVGGVTTPLVLLCCT	RTTNDGURWHISDAD
29	ACTMSPWDPKRE	INNAVACVRCINTTGTAPM	SIVAVSYGCLATCNGC
30	ICSDTSYKRRER	AVAVVVLVSTPPLVLLCCT	FILKMRRA
31	TKDQVNLICITYA	YTTSASAVTFTVPLLSTCVVS	IRCESSAVANRKSIOZR
32	WTLGZGCVATC	LFLPSSSCTVCLTNTVSA	TUWYNGCCEACORPR
33	ACTDGMNTAURH	LRLPSSPTVPLVLLCCT	TCIETJRN
34	RETDTDKSRV	LTTTICVLLTTFVLLCCT	VEHTTLLRCVVKORNA
35	TDVNAKX-PMEYCOV-KO	WVFLGTCICPLVLLCCT	MICDUNRNCRLSIALSCL
36	VCIMPUDKMDYKDUO	WVFLGTCICPLVLLCCT	MICDUNRNCRLSIALSCL
37	SCAFFPSRDLKPK	IMKMASTVTVPLAISVTT	JARLICGASAYNLPVIGCIVKVKQI
38	ACIPTPCBDELKPK	IMKMASTVTVPLAISVTT	JARLICRASAHNLPGCTNEYXKQI
39	TCRSTPSKINRKL	SZEVVSLVCTAVPFSIADVTT	LLARLASSO
40	VCVTCVCAVR	WICMTNSFJPLVLLCCT	VIAMICLIVVHOAALCQCVCTVTRNELEISTJTNMIEPGRV
41	TCVTPPSRSHEV	FWMLNVECTLPLSIIITCTV	DOVLRNEMDQOTKEV
42	SCTKISRNTS	PTTLMDFGTWPLLAVVLLG	ZARLITLNPIPSDPKENSRTDONSZTHONCGVILVA
43	KEVVAHPEDSCLL	LTWLVWALTTPLAVMVVAT	VICL...TWRHAPVCHCANCANLKH
44	VCVTPDPMGRTK	ATKTCVTLTTLPLVIGTAT	WGTTTAAHSEPTGSSRTHCV
45	TCVW-4PCPDKNT	TTMIVVLLVCTPLVLLCCT	TTGTTTGGCPLGTCRMECL
46	VCVTPDQSONLTV	GLCOTNLLCPLVLLCCT	LTMCJLQHETCIGGU
47	DCAVI	ITATLSTVLT-PLVLLCCT	WVKIRRNTHAS
48	ICPMDVTLQ	-VTT-...-IVVAVFLICKI-	KITTFAVRNPMLAIN
49	ICPMDVTLAL	-ATVTVL-...-IVVAVFTVCC-	KITTFAVRNPMLAIN
50	ICPMDVDSPLQ	-LVSPLSIVENLAVVTC-	KITTFAVRNPMLAIN
51	SCDVTTSQEVNNE	STVTTTPTWHTPMLIIFTCT	OLVTVKREAAACGESSA...
52	SCDVTTSQSTPGVQ	STTVLVMCTPLSIVCT-	QWHLAIRAVARCGESE...
53	SCDVTTSQSTPGVQ	STTVLVMCTPLSIVCT-	QWHLAIRAVARCGESE...
54	SCDVTTSQTGTRSE	STNTLTTCTVPLSICCT-	QWHLAIRAVARCGESE...
55	TCGQVIGLQCSDFLND	LWVTFVLLAVPLACITSTF	KIVSSIC
56	TCGQVIGLQCSDFLND	LMILTCIAWVPTVFCVLLSTI	KTCAVL
57	TCGQVIGLQCSDFLND	LSVCFATVPLGSCENLVTSTA	TCVTTI
58	TCGQVIGLQCSDFLND	LCMHWVPLAATSTSCCTST	KIVSSIN
59	TCGQVIGLQCSDFLND	LMIFDST...LPTTFLVEMA	KIVSSIL
60	TCGQVIGLQCSDFLND	LCFVFLT...LPTTFLVEMA	ATCAGM
61	TCGQVIGLQCSDFLND	LWVNGVLT...LPTTFLVEMA	KIVSSIL
62	TCGQVIGLQCSDFLND	LWVNGVLT...LPTTFLVEMA	ATVSSIF
63	TCGQVIGLQCSDFLND	LWVNGVLT...LPTTFLVEMA	KIVSSIL
64	TCGQVIGLQCSDFLND	LWVNGVLT...LPTTFLVEMA	RWVASIL
65	TCGQVIGLQCSDFLND	FMGCVTVL...LPTTFLVEMA	KAVSHAVRIGCCTOKS...INTSDOKVVTAPDA
66	TCGQVIGLQCSDFLND	YLQFLATL...LPTTFLVEMA	RVAVQKUL...LPTTFLVEMA
67	TCGQVIGLQCSDFLND	STT...LPTTFLVEMA	KITTRKLRKRNMMOKIKRDKRS
68	TCGQVIGLQCSDFLND	YIIC...LPTTFLVEMA	KIVSLEKRSARLTRKNTSKRS
69	SCFPTWED	...MFSTT...LPTTFLVEMA	ITPIIRNLSONLZGTRTATYC
70	ACMPLPPEAOHMLV	GTVLT...LPTTFLVEMA	LILABRQVALUGCQCR
71	ACMNO	ISLSTL...LPTTFLVEMA	UNDECRARRO
72	TCVLTVAEVMVLL	SARVLL...LPTTFLVEMA	TTTSTVORTJ
73	TCVGTANTCSCGTPV	FINTVNGCSTPLAHLSTT	RAVFTTNGTVC
74	TCVGTANTCSCGTPV	TLWVTCGAVTPTVSTCTT	RESRIVAVSS

FIGURE 8E

1	KEQHITTCFX	LNTVIVLVCAVFAVYRIVNC	NMTPALVNLKTTI
2	KEVMAKS	LAVICFALCALPHIINNOTTT	CPECSHAPD
3	KELCAKS	LALLTFLALSALPHTLNTCTTS	C7SERGSS
4	( 83) - KEECPHEECLAKRNTSIVWKAART	LSAIIIAITLTNPPIHDLVSTT	CCCPTT
5	( 90) - K-TVQTYX-QPAKQP-PSEKRRVAT	LSAIIIAITLTNPPIHDLVSTT	CACCPAT
6	( 66) - KAFALA-RSTTGRDGSIVLVEKAACT	LSAIIIAITLTNPPIHDLVSTT	CACCPAT
7	( 13) - K-FAST-AUCVADOCY-AAMERRYAT	LSAIIIAITLTNPPIHDLVSTT	CACCPAT
8	( 55) - K-LVNPFSHOTKURGSIVLVEKAACT	LSAIIIAITLTNPPIHDLVSTT	CACCPAT
9	-AAMAAAPLANKACTRPSRLVALEREKALXT	LEIDGIVTCAALPHTPLANWRAF	CRECVPA
10	-KEMKALX	LEIDGIVTCAALPHTPLANWRAF	CONFIRE
11	-VPACTARPLP?IIRNRAET	LEIDGIVTCAALPHTPLANWRAF	CPSLVPS
12	-INCNTFVLLFSREKAACT	LCWCVLQMLPPTLMPCISF	FDPDFSE
13	-ANGNFRRSIAVICJU3REKAACT	LCWCVLQMLPPTLMPCISF	FSLQPCA
14	- (77) - TISARRARASSTCRAVACAREKATV	LAWGIVTCAALPHTPLANWRAF	CREACVPC
15	- (106) - GGT-CALCE-AURAMVTEKRTTV	LAWGIVTCAALPHTPLANWRAF	CPKCVPH
16	- (84) - CACASACLPRRAGCCTNREKRTTV	LAWGIVTCAALPHTPLANWRAF	CCSVPC
17	- (84) - CCGLRAGCAGAEPFGCNGCENFTV	LAWGIVTCAALPHTPLANWRAF	CCSVPC
18	- (167) - KESSEVNTIEXCISLSKERRAK	LCGIVTCAALPHTPLANWRAF	CCSVPC
19	-SPKTRVLT	LSVDEIVTCAALPHTPLANWRAF	CCSVPC
20	-KERVLC	LSVDEIVTCAALPHTPLANWRAF	CCSVPC
21	- (91) - PNECTCSLATSARLSCREKAACT	LAWGIVTCAALPHTPLANWRAF	CCSVPC
22	- (47) - SNGALSTS17LCPGTLPLERATON	VAIVICAUVCMLPPTLWTH	CCSVPC
23	- (29) - ALPPOTPPCTARRAKTTERRAKAT	LPVCAVTCATPPTWHITAL	CCSVPC
24	- (10) - HNVKXLAQCSALERKQISAAERATK	LCGIVTCAALPHTPLANWRAF	CCSVPC
25	- (57) - ASTERCHERAEURQALAREKATV	LCGIVTCAALPHTPLANWRAF	CCSVPC
26	-WPNPOOKTRRUGGERPFTCALINDRAKSV	LCGIVTCAALPHTPLANWRAF	CCSVPC
27	-EPSTAGRDGSISMCRAEAE	LCGIVTCAALPHTPLANWRAF	CCSVPC
28	REKUAVT	DAVNCATTCATPPTDVYRC	CCSVPC
29			
30	-TRESPLRV	LSFVMAINTLQNSP?WALLATV	RUELOMPC
31	-TASTCILAV	VAWAISTTMLPPTVTCIYST	LE233PTE
32	-TFACTNSTV	ALTSAAVTCITPPTVTCIYST	ART3FSTSTIAT
33	-JSEVENPAS	LCGIVTCAALPHTPLANWRAF	PPNPANGACLS
34	-CGRORAHV	ITAWLDTLALPHTPLANWRAF	MEDVIECZCRNHR
35	-ZVRRALDN	VCVIAVTCITPPTVTCIYST	AELCXPISDPCAND
36	-KORREVAC	VTCVIAVTCITPPTVTCIYST	VSDCOPNCE
37	-KORREVAC	VTCVIAVTCITPPTVTCIYST	LYDOSMPFC
38	-ZSKRGLAC	VTCVIAVTCITPPTVTCIYST	RYSEVDSMUV
39	-ZTKRGLAC	VTCVIAVTCITPPTVTCIYST	MYXLDIPSLRM
40	-CERKESRC	ITSVWTFVLCALPHTPLANWRAF	STUNTMPT-CUDALT
41	-CALKNTLV	ITAWLDTLALPHTPLANWRAF	LSZDNTTJLJFHC
42	-TDEKATVL	VIAVTCITPPTVTCIYST	LSQVLSZKARAVDI
43	-SRSKSVTH	LAWVLLPALLPPTVTCIYST	LSSTTFCNMK
44	-OAKGKVK	HPVWVTCITPPTVTCIYST	QEDITGUNFO
45	-SARVWVH	HWVWCJATGCPHTPLANWRAF	NPOLSTXQIO
46	-KARUVVHM	HIVWVTCITPPTVTCIYST	YQUNMBE100
47	-RGOIITK	ITAWLDTLALPHTPLANWRAF	TQCLLROCCEDIVC
48	-HSSKCTTV	ITAWLDTLALPHTPLANWRAF	YVSTCIV
49			
50	-KDTKLARRY	ALDTCIT-CAPISPTAASAF	KVPLTYSKX
51	-CTERIAKRM	AVLDTCT-CAPISPTAASAF	KVPLTYSKX
52	-SOTRIAKRM	AMLTDTL-CAPISPTAASAF	KVPLTYSKX
53			
54	-KAEKEVTRN	VIAVTCITPPTVTCIYST	IGCNTG?
55	-KAEKEVTRN	WWWLAFITCAGPZTACTAA	NPCTPFL
56	-KAEKEVTRN	WWWKFAIT/CAGPZTACTAA	IGCAYAOI
57	-KAEKEVTRN	WWMGSTCVCVPCAFACWVW	IGCBLSLA
58			
59	-MISSVHRC	ATSTCASHLSWSLPTCISLWV	SSAASSSSASA
60	-RVSFAGDM	STT-CSEKAVLCPT-CVLAFT	NPSSSILAGOM
61	-KIPSAAGRMR	ATSTCASHLSWSLPTCISLWV	TSVSESSLSK
62	-SISTVQDK	ATSTCASHLSWSLPTCISLWV	SSAWESSSSASA
63	-RVSFAGDM	STT-CSEKAVLCPT-CVLAFT	C2AGNSTKEY
64	-RVSFAGDM	ATSTCASHLSWSLPTCISLWV	APOLSA
65	-RVSFSTZIK	STT-CSEKAVLCPT-CVLAFT	C7SANTSJES
66	-RVSFSSCDK	ATSTCASHLSWSLPTCISLWV	CPSSANSEKET
67	-RVSFSTZIK	STT-CSEKAVLCPT-CVLAFT	C7SANTSKEY
68	-RVSFVGTDK	STT-CSEKAVLCPT-CVLAFT	CPSSANSTKEY
69			
70	-RQDILRAC	EVLDIWVLLCAGPZTACTAA	CPMCIC
71	-RQDILRAC	EVWVLLALCAGPZTACTAA	SKAINDOG
72	-TDRKRNH	EVWVLLALCAGPZTACTAA	NCI2LZCNG
73	-SENWALLAT	VITVLSVTCITPPTVTCIYST	CPVAC-ILJF
74	-REFKOMS	UTVLSVTCITPPTVTCIYST	WVCPET
75	-SEROMSM	VHVVVTCITPPTVTCIYST	AECCAT
76	-RSAUCLMV	VIAVTCITPPTVTCIYST	WTOIPAF
77	-KCRSPZET	VSVLL-SVALCCTTTSVSLNFNST	AT2AHPHOXJLAC
78	-KAROFKIV	LSVWVTCITPPTVTCIYST	ELLAG-NETZEWIT
79	-RUCRIVVW	LSAIIIAITLTNPPIHDLVSTT	ELLAG-NETZEWIT

FIGURE 8F

7

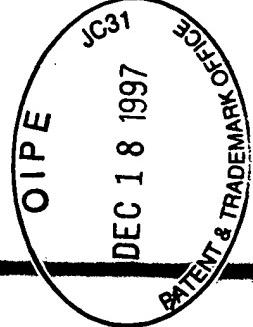
1	SVSAGTASVTTTNPPI-TYTF	CAKILWTTTSTTPTDVKRLLKQXNNPSPPTSSSPTTSQTSQHCPPTDVOCSSDMOCSELXPNMV-(6)
2	YATLTLVLSKNSVNPPI-YATR	IEFECTTAKTTRKSVLRLRERTRACTSARALANGSDCZISLPLNXPCCWANGSAPKPEPPRNNTT-(50)
3	LMLTAFLCHNSAMNPV-YATR	ICKFRVTLKXNDHTKCGPTPPVCEOPPEAPHD
4	EWELQMLTETVNSTINPHE-YALC	NKAUTROTTRLLIWRDQWHRKSKRACPCVSPCC
5	WTCIGMLTCTNSTINPAC-YALC	NAITKTKTQDLCMTCAT
6	TMNLTCLETNSTVNPFV-YALC	NKTTGTTK...L...CQKQURQOCRSVTFHKGVPICAL
7	WMSICHTLCTNSTINPAC-YALC	NAITKTKTTRC...CTRYNIDAR
8	UMLTQMLTCTNSTVNPFV-YALC	NKETKTKTTRM...L...CQKQURQVLELTHQNSKLP
9	UFVTTMLTCTANSANPPI-YCFS	PDTRXAFCCLL...ARRAARRAHTHCRPASCCLARPCTPSPGQUSCDDOOGVGA?PARLTPHACCN-(25)
10	VVILLWCTNSTVNPFV-YCFS	PDTRXAFCCLL...CARSLSXAVATCCTSSNGCTTSDVCEKNCCLDULCTEDFGCQCTVPSENID-(13)
11	AFLALMLTCTANSANPPI-YCFS	PDTRXAFCCLL...CQKQURQOCRSVTFHKGVPICAL
12	VFKLALMLTCTANSANPPI-YCFS	SQEFKUAFQMVLAQCRKKSQYLT...TAPSHVLESCCKOLVRIPVGSAUETTNCSDQDNCEKIF-(66)
13	VFKLALMLTCTANSANPPI-YCFS	SKEFKUAFQMVLAQCRKKSQYLT...TAPSHVLESCCKOLVRIPVGSAUETTNCSDQDNCEKIF-(66)
14	LFQFTTMLTCTANSANPVI-TTFT	MDFRAPSFIKLLFARRACTR
15	LFQFTTMLTCTANSANPVI-TTFT	MDFRAPSFIKLLFARRACTR
16	LFQFTTMLTCTANSANPVI-TTFT	MDFRAPSFIKLLFARRACTR
17	LFQFTTMLTCTANSANPVI-TTFT	MDFRAPSFIKLLFARRACTR
18	FNTTMLTCTANSANPVI-TTFT	MDFRAPSFIKLLFARRACTR
19	ITDVTWTCGANSANPVI-YA-F	NADFRKAFT...L...CQKQURQVLELTHQNSKLP
20	ITDVTWTCGANSANPVI-YA-F	NADFRKAFT...L...CQKQURQVLELTHQNSKLP
21	LYSAFTTCTANSAVNPVII-TTT	NIEFRKAFTKLKHC
22	LYSAFTTCTANSAVNPVII-TTT	NIEFRKAFTKLKHC
23	LYSAFTTCTANSALNPVII-TTFT	NIEFRKAFTKLKHC
24	LFDTTMLTCTANSALNPVII-TTFT	NIEFRKAFTKLKHC
25	LGADMLCVLDSLNPVII-YATF	NIEFRKAFTKLKHC
26	LNWVWHTCTCSLNPVII-TTFT	NIEFRKAFTKLKHC
27	LNWVWHTCTCSLNPVII-TTFT	NIEFRKAFTKLKHC
28	LEAVTMLTCTANSALNPVII-YATL	NIEFRKAFTKLKHC
29	AVIDTSLALTNSCANPVI-TVFM	CDFPRFLKHLPAFLSLALTDSTTSDTANSILPVAEVALAK
30	LDLSLKVSTAYTDSNCPPI-YVFM	CDCFOGRALKSLSPTLAVWLTESWREKSITFSTVOTMAGKCAV
31	AYLCCVGSISSTCNPPI-YVFM	SSCCTCYTSL...L...CQKQURQVLELTHQNSKLP
32	-LITLTIVATWQDLPV-YTFL	RAVRLRLOPFLSTAPRSLSLCPOLTCSCLO
33	ADASLLGILGSLCNPPI-YATI	CONTRMGLKTLASHGLLSDSPKPSRSTSVCSSGEST...
34	ANQFCLCISVCDLPV-YCFL	DQFHQKLSLQKRSRRESRSTV...L...CQKQURQVLELTHQNSKLP
35	HOTIGLNLATCNSCNPPIALITYS	KUFKNCITOSC...TOSXSIMSVPHGSIQHNGDQHHTERSHGDSTN
36	LDTIGLNLATCNSCNPPIALITYS	IRPFKNCITOSC...TOSXSIMSVPHGSIQHNGDQHHTERSHGDSTN
37	TICARLLAPDNCVNPFAFLYLS	KSFPRJNTLQCPUDKRSMSK...GTCMTCSTKSTPNSAITSLLNGMTCSTV
38	VTLVAVRLSTFSNCVNPFAFLYLS	ESFRQHSMQK...KSTPNSAITSLLNGMTCSTV
39	ALVTOCLSLVNCVNPFAFLYLS	MRNTRQFSLVAFIKRISAKTGLDASRSETTISALQNAK
40	FIMDQFLTVSAINPIL-YNLV	SANTROVLTSLAC...L...CQKQURQVLELTHQNSKLP
41	VQISSTTATNSCNPVII-YTIV	GIOFRQGSEVYCALCNGK...GSEVYOPENPCTAISLVDRIHQGCDHAGKQ
42	-LUEKICLTVSAINPIL-YNLV	SOKRKAFTFLRCPPTVYDODKLE...L...CQKQURQVLELTHQNSKLP
43	VTLAFLMAMSTCNPPI-YCFL	MDFRFLKHLPAFLSLALTDSTTSDTANSILPVAEVALAK
44	VTLAFLMAMSTCNPPI-YCFL	MDFRFLKHLPAFLSLALTDSTTSDTANSILPVAEVALAK
45	AMPDCLCLATQONLNPFL-YCFL	MDFRFLKHLPAFLSLALTDSTTSDTANSILPVAEVALAK
46	DRBISLSTTNSCNPPI-YTIV	CSSTQJQRFKLSLWVLRPAPDTEPQAPDQNE-MTIVTCW.
47	VLLVLFPTI-NUSCNPFL-YATF	TXTDXOFF...L...CQKQURQVLELTHQNSKLP
48	ILVLVLFPTI-NUSCNPFL-YATF	TXTDXOFF...L...CQKQURQVLELTHQNSKLP
49	ILVLVLFPTI-NUSCNPFL-YATF	TXTDXOFF...L...CQKQURQVLELTHQNSKLP
50	PRCPAFTTAACTTNPVI-YDPM	MICFRNCHL...CQKQURQVLELTHQNSKLP
51	MAALPAFTTAACTTNPVI-YDPM	MICFRNCHL...CQKQURQVLELTHQNSKLP
52	MAALPAFTTAACTTNPVI-YDPM	MICFRNCHL...CQKQURQVLELTHQNSKLP
53	LVTIPSFTSKSACTTNPPI-YCPM	MICFRNCHL...CQKQURQVLELTHQNSKLP
54	-DASVETTWTAVNPPI-YSL-	RNDQVKSVLQK...L...CQKQURQVLELTHQNSKLP
55	AAAVPENWTPMNPPI-YSL-	RNSDPMKAALRKLAMRPFPSKQ
56	-ATVPLNTWTPMNPPI-YSL-	RNCVKAALRKLREVKX
57	-EASVPTTWTPMNPPI-YSL-	RNCVKAALRKLREVKX
58	-PRAPPTTWTPMNPPI-YSL-	RNCVKAALRKLREVKX
59	-LVSMLIAVPLNPPI-YSL-	RNCVKAALRKLREVKX
60	-AHPAFTTWTPMNPPI-YSL-	RNCVKAALRKLREVKX
61	-WISLMLIAVPLNPPI-YSL-	RNCVKAALRKLREVKX
62	-AHPAFTTWTPMNPPI-YSL-	RNCVKAALRKLREVKX
63	-WISLMLIAVPLNPPI-YSL-	RNCVKAALRKLREVKX
64	WTACSMCLCINSTVNPIII-YALR	RNCVKAALRKLREVKX
65	LTAJNHTAFLS...NPPI-YCFL	MDTFLKXLLAHLSCRRPPKZDRLPSPVPSFRVANTEXKCRAPLPMQHLPSSCIGSQCJLSSVEPWMS
66	LFLLCHLDMSTCNPPI-YCFL	MDTFLKXLLAHLSCRRPPKZDRLPSPVPSFRVANTEXKCRAPLPMQHLPSSCIGSQCJLSSVEPWMS
67	AETIV-LAVLNSCNPPII-YTCI	MCFRFLKHLPAFLSLALTDSTTSDTANSILPVAEVALAK
68	AMCGLLSTTNSCNPVII-YACK	MCFRFLKHLPAFLSLALTDSTTSDTANSILPVAEVALAK
69	VSOLSVLSTTNSCNPVII-YCFL	MCFRFLKHLPAFLSLALTDSTTSDTANSILPVAEVALAK
70	PETVDELCIYESSAKNPVII-TTIA	SCNTKSRFORL...L...CQKQURQVLELTHQNSKLP
71	IGLARVWPKCLNPFL-YALL	GRKSRQHMEP...L...CQKQURQVLELTHQNSKLP
72	CEVQHFLATVRAECPGII-YIIV	GTQFLCRPACTRCQDLDRAFLRSONCRA
73	ALMSTTAACTTNPPI-YTIV	GTQFLCRPACTRCQDLDRAFLRSONCRA
74		GTQFLCRPACTRCQDLDRAFLRSONCRA

FIGURE 8G

## INTERNATIONAL SEARCH REPORT

Int. application No.

PCT/US93/08528

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) :C07K 7/00, 15/06; C12N 15/12  
 US CL :435/69.1; 514/12, 13, 14, 15, 16, 17; 530/387.9

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/69.1; 514/12, 13, 14, 15, 16, 17; 530/387.9

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN/MEDLINE

search terms: G protein coupled, receptor#, fragment#

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NATURE, Vol. 336, issued 22 December 1988, J. R. Bunzow et.al., "Cloning and expression of a rat D2 dopamine receptor cDNA", pages 783-787. See entire document.	1-41
A	Biochemistry, Vol. 26, No. 10, issued 19 May 1987, H. G. Dohlman et.al., "A Family of Receptors Coupled to Guanine Nucleotide Regulatory Proteins", pages 2657-2664. See entire document.	1-41
A	BIO/TECHNOLOGY, Vol. 7, issued September 1989, S. Marullo et.al., "EXPRESSION OF HUMAN B1 AND B2 ADRENERGIC RECEPTORS IN E. COLI AS A NEW TOOL FOR LIGAND SCREENING", pages 923-927. See entire document.	1-41

Further documents are listed in the continuation of Box C.  See patent family annex.

• Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be part of particular relevance		
*E* earlier document published on or after the international filing date	X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed	A	document member of the same patent family

Date of the actual completion of the international search

25 October 1993

Date of mailing of the international search report

DEC 02 1993

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Authorized officer

JOHN D. ULM

Facsimile No. NOT APPLICABLE

Telephone No. (703) 308-0196